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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-040722 |
| Article Type: | Original research |
| Date Submitted by the Author: | 21-May-2020 |
| Complete List of Authors: | Capion, Tenna B.; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Lilja-Cyron, Alexander; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Juhler, Marianne; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Mathiesen, Tiit; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Wetterslev , Jørn; Copenhagen University Hospital, Rigshospitalet, Copenhagen Trial Unit; Copenhagen University Hospital, Rigshospitalet, Copenhagen Trial Unit |
| Keywords: | NEUROSURGERY, INTENSIVE & CRITICAL CARE, NEUROLOGY |
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# Prompt closure vs. gradual weaning of external ventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid haemorrhage: A systematic review

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**Keywords/MeSH terms:** Subarachnoid Hemorrhage/complications, Aneurysm, Hydrocephalus, Treatment outcome

**Word count:** 5885

## 1. ABSTRACT

**Objectives:** To summarize the evidence on benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aneurysmal subarachnoid haemorrhage (aSAH) based on randomized clinical trials in humans.

**Setting:** Randomized, clinical trials (RCT) comparing prompt closure vs. gradual weaning of external ventricular drainage in adult patients with hydrocephalus following aSAH were included.

**Participants:** Patients aged equal to or greater than 18 years with an external ventricular drain (EVD) due to hydrocephalus following aSAH were eligible for inclusion.

**Primary and secondary outcome measures:** Primary outcomes were all-cause mortality, any serious adverse event, rate of ventriculo-peritoneal (VP) shunt placement and quality of life. Secondary outcomes were patients with shunt failure, hospital and Neuro Intensive Care Unit (NICU) length of stay (LOS) and complications related to treatment with an EVD. Data permitted report of rate of VP shunt placement, and hospital and NICU LOS.

**Results:** Six studies were assessed in full-text. One RCT with 81 patients was included. Rate of VP shunt placement was 63.4 % in the rapid weaning group (i.e. prompt closure of the EVD; 41 patients) and 62.5% in the gradual weaning group (40 patients; $p = 0.932$). LOS in hospital and NICU was significantly shorter in the rapidly weaned group compared to the gradually weaned group (mean 19.1 vs. 21.5 days in hospital [$p = 0.03$]; and mean 14.1 vs. 16.9 days in NICU [$p = 0.0002$]). Data was insufficient to conduct meta-analysis, trial sequential analysis or subgroup analysis of heterogeneity and sensitivity. One RCT is currently ongoing.

**Conclusions:** We found insufficient evidence to favor any of the two strategies for EVD discontinuation in patients with hydrocephalus following aSAH.

**Trial registration:** This systematic review was preceded by a published protocol and is registered in the PROSPERO register under the ID number CRD42018108801

## 2. ARTICLE SUMMARY

Strengths and limitations of this study

Strengths

1) Patient centered outcomes
2) Rigorous assessment of bias and the risk of random errors
3) GRADE assessment of the quality of the total evidence

Limitations

1) One included RCT
2) Recommendations from systematic reviews may suffer from the quality of the included trials

## 3. PLAIN LANGUAGE SUMMARY

Discontinuation of external ventricular drainage to treat secondary acute hydrocephalus in patients with hydrocephalus following aneurysmal subarachnoid haemorrhage (aSAH) is controversial despite the frequency of the treatment. Typically one of two strategies is being followed; prompt closure or gradual weaning, the latter in which resistance to drainage outflow is increased over days.

This systematic review aimed at summarizing the evidence on benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH based on randomized clinical trials in humans. We identified one small randomized, clinical trial (RCT) with 81 patients, which reported no difference in rate of ventriculo-peritoneal (VP) shunt placement, but longer hospital and Neuro Intensive Care Unit (NICU) length of stays in the gradually weaned group. The included RCT was assessed to have a high overall risk of bias mainly due to high risks of performance bias and reporting bias together with unclear risks of bias in the remaining areas of bias assessment.

The authors of this review conclude that there is insufficient evidence to favor either of the two investigated strategies for discontinuation of external ventricular drainage in patients with hydrocephalus following aSAH. One RCT comparing the two strategies is currently ongoing.

## 4. BACKGROUND

Aneurysmal SAH (aSAH) is a common and often devastating cerebrovascular disease accounting for approximately 7 % of all strokes.(1) Acute hydrocephalus due to blockage of cerebrospinal fluid (CSF) circulation occurs as a common and severe complication, which is treated with an external ventricular drain (EVD) in the acute phase. An EVD enables removal of CSF and subsequently management of intracranial pressure (ICP).(2,3) Up to 37 % of patients with an EVD develop chronic hydrocephalus during the course of the disease, requiring permanent diversion of CSF via a ventriculo-peritoneal (VP) shunt.(2) How to increase safety of EVD discontinuation and reduce the need for a VP-shunt is debated. Two different strategies are typically being used to assess for dependence of drainage; prompt closure or gradual weaning of the EVD. The latter is performed by stepwise increase of drainage resistance to outflow over days. It is unknown whether these two strategies result in differentiated clinical outcomes, different risks for VP shunt placement or whether they lead to different complication rates of EVD and VP-shunt treatment.

### 4.1 Description of the condition

In adults, CSF production is constant at approximately 500 ml/day. Thus CSF circulation and absorption occur at a similar rate keeping the system in balance. Post-haemorrhagic hypersecretion of CSF or obstruction of CSF circulation and absorption result in hydrocephalus.(4) The reported prevalence of hydrocephalus following aSAH ranges between 6 % and 67 %, and three stages of hydrocephalus are generally recognized: acute (0-3 days after SAH), subacute (4-13 days after SAH) and chronic ($\geq$ 14 days after SAH).(3)

### 4.2 Description of the intervention

Scientific data to define timing and choice of strategy for discontinuation and removal of an EVD inserted to treat hydrocephalus following aSAH is sparse. In some patients circulation of CSF returns to normal within days or weeks, permitting the EVD to be removed with ICP within normal range and no further need for treatment. In other patients, chronic hydrocephalus evolves with the need for an implanted permanent drainage solution (a VP shunt)(5) which diverts CSF from the brain ventricles to the abdomen where it is absorbed. Prolonged duration of EVD treatment as seen in gradual weaning of the EVD is an attempt to await potential return of normal CSF circulation and thereby avoid a permanent shunt. However, the risk of serious and potentially fatal infection (ventriculitis, meningitis, cerebral abscess) increases with prolonged EVD treatment. Conversely, early discontinuation may involve risks associated with increased ICP and acute hydrocephalus and possibly increased risk for placement of a permanent shunt.

### 4.3 How the intervention might work

The process of identifying patients who will need a permanent VP shunt involves a trial of closure of the EVD. The main argument in favour of prompt closure of the EVD is to minimize the treatment period and thereby the risk of infection. Subsequently, patients could potentially be discharged earlier from the hospital and thus begin rehabilitation sooner. The arguments in favour of weaning by gradually increasing drainage resistance involves time for reestablishment of normal CSF circulation, and thus less drastic changes in ICP with potential protection of brain tissue.

### 4.4 Why it is important to do this review

A possible difference between the two treatment strategies is important to identify as difference in treatment may affect patient outcomes. Insertion of a VP shunt is best defined as a surrogate outcome measure in the present context, as the indication for the procedure seems to vary throughout and the procedure is associated with risks for the patient (i.e. mechanical shunt dysfunction and shunt related infections) and increased medical costs for society as shunt complications frequently require additional hospitalizations and surgical interventions.

Previous reviews within this field have compared the two EVD discontinuation strategies in patients with hydrocephalus following aSAH via comprehensive literature searches without pre-published protocols or pre-defined hypotheses or data extraction plans, and without a validated rating of the available evidence.(6,7) A review that methodologically meets the rigorous demands for systematic reviews as defined by the PRISMA guidelines (and 2015 PRISMA-P statement) provides the highest possible impact for researchers to use in forthcoming work and investigation of this medical issue.(8)

## 5. OBJECTIVES

To summarize the evidence on benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH based on randomized clinical trials in humans.

# 6. METHODS

## 6.1 Criteria for considering studies for this review

### 6.1.1 Types of studies

This systematic review was conducted in accordance with PROSPERO registration (CRD42018108801) and a pre-published protocol.(9) The recommendations from the Cochrane Collaboration, the PRISMA guidelines for systematic reviews (8) and the GRADE assessment were followed.(10)

Randomized clinical trials (RCT) comparing prompt closure vs. gradual weaning of external ventricular drainage in patients with aSAH were included in qualitative evaluations of intervention effects in this systematic review. Additionally, findings from observational studies were included in an appendix describing serious adverse events (SAE).
Studies were assessed without consideration of publication status, blinding status or language. No unpublished trials or trials using quasi-randomization were included.

### 6.1.2 Types of participants

Patients aged equal to or greater than 18 years with an EVD due to hydrocephalus following aSAH were eligible for inclusion.

### 6.1.3 Types of interventions

Interventions studied involve prompt closure, i.e. the direct closure of the EVD, vs. gradual weaning, i.e. a gradual increase of resistance to outflow over days, of external ventricular drainage due to hydrocephalus following aSAH.

### 6.1.4 Types of outcome measures

Predefined primary outcomes include death from any cause, any SAE defined according to the International Conference of Harmonization of Good Clinical Practice (ICH-GCP)(11), complications and adverse events specific for EVD and VP shunt systems (clinical and radiological signs of shunt obstruction, and clinical and microbiological signs of ventriculitis and shunt infection), rate of permanent VP shunt placement and quality of life measured (QoL) with any score.
Secondary outcomes comprise number of shunt interventions following the primary shunt insertion (surgical shunt interventions for any reason) within the longest follow-up in each trial, total hospital and NICU length of stay (LOS), and EVD related complications (ventriculitis defined as positive CSF culture,

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

### 6.2 Search methods for identification of studies

#### 6.2.1 Electronic searches

Searches were performed without language or date restrictions. The following electronic databases were searched: The Cochrane Library's Central Register of Controlled trials (CENTRAL), MEDLINE (1946 to date) (Ovid SP), EMBASE (1974 to date) (Ovid SP), LILACS (1982 to date) (BIREME), Science Citation Index Expanded (1900 to November 2018) and Conference Proceedings Citation Index – Science (1990 to November 2018) (Web of Science). The preliminary search was performed on November 28th 2018 and repeated on January 20th 2020. The search strategies can be seen in Appendix 1.

#### 6.2.2 Searching other resources

Studies included in the full text screening were hand searched for supplemental studies not registered in the electronic searches. Main authors of studies were contacted for any missed, unreported or ongoing trials and to retrieve relevant data.

### 6.3 Data collection and analysis

Main authors of included studies were contacted in case their publication did not contain sufficient information for risk of bias assessment and data extraction of our chosen outcomes.

#### 6.3.1 Selection of studies

Two review authors (TC and ALC) independently evaluated all relevant references and provided a detailed description of included and excluded trials.

#### 6.3.2 Data extraction and management

Titles and abstracts were screened in order to identify studies that were eligible. TC and ALC independently extracted and collected data using the Covidence software (*Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia*). We were not blinded to the author, institution or the publication source of trials. Disagreements were resolved by JW.

Main authors of the included trials were contacted for additional information relevant to the review's outcomes measures and risk of bias components.

### 6.3.3 Assessment of risk of bias in included studies

TC and ALC independently conducted the assessment of risk of bias using The Cochrane Collaboration's recommended tool for assessing risk of bias. Disagreements were resolved by JW.

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. 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 of the quality of evidence for the results of each outcome.(12)

### 6.3.4 Measures of treatment effect

Mortality, SAE, rate of VP shunt placement and number of EVD-related complications are dichotomous outcomes and reported as relative risks (RR) with 98 % confidence intervals (Cis). For mortality, the Peto OR (POR) is calculated. QoL and total LOS in NICU and hospital is measured as continuous outcomes with the intervention effect as standardized mean difference with 98 % CI. Additionally, risk difference (RD) with 98 % CI and subsequently numbers needed to treat is measured.

### 6.3.5 Unit of analysis issues

Number of events is used in all binary analyses. Standardized mean difference is used in analyses of continuous data. QoL is measured with any score used in QoL analyses. SAE is a composite outcome measure comprising the number of patients with one or more SAE.

### 6.3.6 Dealing with missing data

Main authors of included trials were contacted in order to retrieve missing data.

Modified intention-to-treat (ITT) analysis to minimize bias in the design, follow-up and analysis of the efficacy of randomized clinical trials is attempted.(13) Full application of ITT is possible only when complete outcome data are available for all randomised patients. Even though about half of all published reports of RCTs 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.(14) In cases of missing data for our primary outcomes a 'complete-case analysis' is used by excluding all participants with the outcome missing from analysis. Additionally, sensitivity analyses for our primary outcomes are applied via best-case and worst-case scenarios (please, see section on sensitivity analyses).

### 6.3.7 Assessment of heterogeneity

The degree of heterogeneity observed in the results is quantified using diversity ($D^2$)(15) 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).(16) 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 ≥75 %, respectively.(16)

### 6.3.8 Assessment of reporting biases

Publication bias occurs when the publication of research results depends on their nature and direction.(17) We 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.(18) 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 favorable outcome. Relationships between industry, scientific investigators and academic institutions are widespread and often result in conflicts of interest.(19,20)

### 6.3.9 Data synthesis

Due to the number of primary outcomes, we adjust the level of statistical significance and CI's due to statistical multiplicity to keep the familywise error rate (FWER) below 0.05. The adjustment is done according to halfway between a full Bonferroni adjustment, and no adjustment, to an $\alpha=0.02(0.05/((4+1)/2))$ and 98 % CI's. We calculate the RR with 98 % CI for dichotomous variables (binary outcomes). We calculate the risk difference, and if the results are similar we will only report the RR.

Additionally, we calculate mean difference as the measure of absolute change with 98 % CI for continuous outcomes. We will use $D^2$ (24) and $I^2$ statistics(16) to describe heterogeneity among the included trials.

If $I^2$=0, we will report the results using the fixed-effect model (FEM) only. In the case of $I^2$>0, we will report the results using both the random-effects (REM) 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 emphasize 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.

Review Manager Software *(Review Manager (RevMan) [Computer program], version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014*) was used as statistical software.

### 6.3.10 Meta-analysis

Conventional meta-analysis of outcomes can be conducted with comparable effect measures where more than one trial is included. The meta-analysis is reconsidered in the case of large clinical and statistical heterogeneity. Causes of substantial heterogeneity can be explored by subgroup analyses and meta-regression using comprehensive meta-analysis. The $X^2$-test will provide an indication of heterogeneity between studies, where $p \leq 0.10$ is considered significant. Adverse effects may be rare but serious, and hence important when meta-analysis is applied for combining results from several trials with binary outcomes.(21) Sensitivity analysis is performed by applying empirical continuity corrections to our zero event trials by applying an imaginary small mortality in both arms in order to make up for overestimation of a treatment effect if RR and CI are exempted. In this case we will apply the POR in the case of small event proportions.(22,23)

Required information size to provide reliable meta-analysis and TSA on our chosen outcomes was not reached in this systematic review and it was impossible to conduct subgroup and sensitivity analyses to investigate reasons for heterogeneity. Please, see published protocol for details regarding the intended meta-analysis.(9)

### 6.3.11 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.(15,24–27) 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 boundaries(28) 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. 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. Trial sequential analysis (TSA) is applied as it prevents an increase in the risk of type 1 errors (<5 %) due to potential multiple updating and early testing on accumulating data, whenever new trial results are included in a cumulative meta-analysis.(29,30) Additionally, TSA provides important information regarding the need for additional trials and their required sample size.(15,27)

Required information size to provide reliable meta-analysis and TSA on our chosen outcomes was not reached in this systematic review and it was impossible to conduct subgroup and sensitivity analyses to investigate reasons for heterogeneity. Please, see published protocol for details regarding the intended TSA.(9)

### 6.3.12 Subgroup analysis and investigation of heterogeneity

To compare intervention effects in patient subgroups, analyses of specified subgroups and investigation of heterogeneity was planned. Required information size to provide reliable meta-analysis and TSA on our chosen outcomes was not reached in this systematic review and it was impossible to conduct subgroup and sensitivity analyses to investigate reasons for heterogeneity. Please, see published protocol for details regarding the intended subgroup analysis.(9)

### 6.3.13 Sensitivity analysis

To assess the potential impact of the missing data for continuous and dichotomous outcomes, sensitivity analyses were planned in the form of best-worst-case and worst-best-case scenarios. RR with 98 % CI and a complete case analysis for the sensitivity and subgroup analyses based on the mortality and SAE primary outcomes were planned. Required information size to provide reliable meta-analysis and TSA on our chosen outcomes was not reached in this systematic review and it was impossible to conduct subgroup and sensitivity analyses to investigate reasons for heterogeneity. Please, see published protocol for details regarding the intended sensitivity analysis.(9)

### 6.3.14 GRADE

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate and assess the quality of the evidence for each outcome.(10) A summary of findings table was produced summarizing the quality of evidence for each outcome.

## 7. RESULTS

### 7.1 Description of studies

#### 7.1.1 Results of the search

We identified 751 references via a primary search in November 2018 and an updated search in January 2020. Fifty-six references were removed as duplicates, leaving 695 to be screened for title and abstract. Of these, 6 studies were assessed in full-text. We found one RCT which met the inclusion criteria(31) (figure 1). We found no studies describing prompt closure vs. gradual weaning of external ventricular drainage in other conditions such as spontaneous intracranial hemorrhage.

#### 7.1.2 Included studies

The included RCT by Klopfenstein et al. from 2004 (31) randomized 81 adult patients with hydrocephalus following aSAH to either rapid or gradual weaning of the EVD. A rapid wean signified prompt closure of the EVD at time of intervention, whereas gradual weaning comprised four steps of increasing drainage resistance to outflow ending at complete closure of the EVD. Of the 81 randomized patients, 41 were in the rapidly weaned group and 40 patients were in the gradually weaned group. The primary outcome of this trial was rate of VP shunt placement. Secondary outcomes were i) number of days in which the EVD was in place; ii) number of days the patient spent in the ICU; and iii) overall duration of hospital stay.
All patients who failed either form of EVD discontinuation underwent shunt placement, resulting in equal shunt rates for the two groups. In the gradually weaned group the EVD remained in place for significantly longer time, while LOS in hospital and NICU were significantly longer for the gradually weaned group. No data were available for death by any cause, SAE or QoL at longest follow-up.
The authors concluded that gradual weaning provides no advantage over prompt closure in terms of rate of VP shunt placement, and that prompt closure should as such be pursued in the treatment of patients with aSAH due to shorter LOS in hospital and NICU and shorter time with EVD in place.
Contact by email to the corresponding and last author of this study in order to retrieve additional relevant data was attempted without result.

One observational cohort study comparing prompt closure vs. gradual weaning of EVD treatment in patients with aSAH was included in an appendix enumerating adverse effects (Appendix 2).(32) The study by Jabbarli et al. from 2018 compared treatment effects in two individual German institutions using different discontinuation strategies for external ventricular drainage in patients with aSAH. Outcomes were development and timing of shunt dependency. The authors concluded that patients treated by rapid weaning (i.e. prompt closure) of the EVD had significantly higher risk of getting a VP shunt and that gradual weaning led to longer EVD treatment but not in the expense of higher risk of drain related infections. Contact by email to the corresponding author of this study in order to retrieve additional relevant data was attempted without result.

### 7.1.3 Excluded studies

Of the six studies included in the full-text screening, five studies were excluded.

One study was excluded due to wrong study intervention. The randomized, clinical trial by Olson et al. from 2013 compared continuous vs. intermittent external ventricular drainage in patients with an EVD due to hydrocephalus following aSAH. The study was terminated after the inclusion of 60 patients due to a higher complication rate in the continuous drainage group.(33)

Two of the excluded studies were conference papers to which full-texts were not available. In one of these studies, authors carried out a prospective, randomized pilot study to determine the feasibility of randomizing patients with an EVD after aSAH to either aggressive or conventional external ventricular drainage. The authors included 20 patients of which 13 were in the aggressive arm, and concluded that randomization is possible. The corresponding author to this study has via email informed that completion of the article was not pursued, nor was further progression with an RCT.
The second study was an abstract of a retrospective assessment of 200 patients with an EVD due to non-traumatic (aneurysmal) SAH(34) comparing gradual wean and early clamp trial of the EVD. The authors compared rate of VP shunt placement, NICU and hospital LOS, EVD duration and rate of EVD related infections and concluded that an early clamp trial was associated with fewer complications and shorter LOS compared to gradual weaning.

The last two references were excluded due to wrong study design; one was an observational study(32) carried out in 2018 which evaluated the role of EVD weaning on rate of VP shunt placement in 965 patients with aSAH. The authors concluded that at the expense of longer treatment, gradual EVD weaning may decrease the risk of shunt dependency without an additional risk of CSF infection. The second reference

omitted due to wrong study design was a comment to the study by Jabbarli et al.(32), featured in the end of the article as contribution.

Details of the 5 excluded studies can be seen in appendix 3.

### 7.2 Risk of bias in included studies

Using the Cochrane Collaboration's tool for assessing risk of bias we found that the included study had limitations in design and execution severe enough to downgrade the quality of evidence. No information regarding allocation table or concealment was provided which resulted in unclear risk of selection bias. Participants and personnel were not blinded to the intervention due to the nature of the intervention. Patients were randomized at time of enrollment. The timing of intervention was decided by a treating physician not involved in the trial execution but blinded to the outcome of the randomization. No details describing how the randomization process was performed were provided. We assessed the risk of performance bias and detection bias as high.

Outcome was reported for the 51 patients out of 81 who received a VP shunt. Follow-up status for the remaining 30 patients was not reported. Intent-to-treat analysis was described for the primary outcome but not for secondary outcomes. The numbers of eligible, included and excluded patients were provided. The reasons for patient exclusion and withdrawal were not specified, neither was information about the handling of the excluded patients in terms of randomization or intention-to-treat analysis. The risk of attrition bias was due to these limitations assessed as unclear. Further, patient-centered outcomes such as mortality, number of SAE, complications related to EVD and VP shunt treatment and QoL were not reported which made risk of reporting bias high. No study protocol was published before the study paper and no sample size calculations were provided which might have led to data driven reporting bias.

These limitations are severe in their generation of the overall risk of bias as they might individually and combined cause bias to the execution of the study and to the randomization process which may cause systematic bias in the inclusion and division of patients and thus to the results of the study. Based on the assessed domains the overall risk of bias of the included study was assessed as high (figure 2).

### 7.3 Effects of interventions

The only primary outcome for which the included RCT provided data was rate of VP shunt placement. All patients who failed either form of EVD discontinuation underwent shunt placement, resulting in a shunt

rate of 63.4 % and 62.5 % for rapid or gradual wean, respectively (*p = 0.932*). Certainty for this outcome assessed via the GRADE approach was considered very low primarily due to very serious risk of bias, very serious imprecision and serious indirectness.

Secondary outcomes for which data were available were time with EVD in place, and hospital and NICU LOS. In the rapidly weaned group the EVD remained in place for significantly shorter time compared to the gradually weaned group (mean of 12.7 vs. 15.8 days, *p = 0.000009*). LOS in hospital and NICU was also shorter for the rapidly weaned group (19.1 vs. 21.5 days in hospital [*p = 0.03*]; 14.1 vs. 16.9 days in NICU [*p = 0.0002*]). The certainty for these outcomes was equally considered very low based on very serious risk of bias, very serious imprecision and serious indirectness.

The power of the included RCT (81 patients) does not reach required information size (RIS) to conduct a reliable and conclusive meta-analysis which in size is expected to be at least that of the sample size of one well-powered RCT for a reliable detection or rejection of an anticipated intervention effect.(15) A study with few patients and few events, and thus wide confidence intervals, raises imprecision and uncertainty about the results, as is also the result in the present included RCT.

### 7.4 Patient and public involvement

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

### 7.5 Ethics and dissemination

The evidence on the benefits and harms of the two common strategies for EVD discontinuation in patients with hydrocephalus following aSAH is sparse, and no methodologically thorough systematic review has been conducted until this point. Results from this review will be published internationally according to the interest of the society. No possible impact, harm or ethical concerns are expected due to this review.

The protocol for this systematic review was published before the conduction of the review which makes it possible for other peer reviewers and editors to be able to measure the completeness and transparency of this systematic review.

## 8. DISCUSSION

This systematic review aimed at assessing the evidence of benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH. We conducted an extensive literature search which resulted in just 6 studies evaluated in full text. We included one RCT with

81 patients which concluded that prompt closure is safe and reduce LOS in hospital and NICU. We assessed however the RCT by Klopfenstein et al. to be of overall low quality with high risk of bias and thus insufficient in order to provide high-quality evidence to support or refute either of the two investigated strategies for EVD discontinuation. Despite the assessed quality of the RCT, the current international guidelines covering this issue base their recommendations solely on the results from this study.(35) Previous reviews differ in design and methodology, they do not assess the quality of included studies in detail, and they support the recommendations for prompt closure as discontinuation strategy despite the above mentioned shortages in evidence.(6,7) There is currently no high-quality evidence to cover this information gap.

The present systematic review is the first of its kind to address the question of EVD discontinuation strategy after aSAH by assessment of included studies using the Cochrane risk of bias tool and the GRADE approach, and it disagrees with previous review conclusions on the applicability of the results of the included RCT in international recommendations and guidelines.

### 8.1 Summary of main results

One RCT with 81 patients was included in this systematic review. The included trial showed very serious risk of bias and imprecision and an overall very low quality assessment based on the GRADE approach and the Cochrane risk of bias tool. Required information size to provide reliable meta-analysis and TSA on our chosen outcomes was not reached and it was impossible to conduct subgroup and sensitivity analyses to investigate reasons for heterogeneity.

### 8.2 Overall completeness and applicability of evidence

There is insufficient evidence to favor any of the two investigated strategies for discontinuation of external ventricular drainage in patients with hydrocephalus following aSAH.

### 8.3 Quality of the evidence

Based on GRADE the certainty of the evidence for the primary outcome and the two secondary outcomes, for which data was provided, was in all cases assessed as ‘very low’. These assessments were mainly based on very serious risk of bias, very serious imprecision and serious indirectness (figure 3).

For the remaining 3 primary outcomes and 2 secondary outcomes which this systematic review sought to evaluate there were no available data.

### 8.4 Potential biases in the review process

The authors to this review has based on the preliminary literature search in November 2018 initiated and launched an RCT comparing prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH which is currently ongoing. We might as such be biased in assessing methods within this field as we have previously done extensive literature search within this area of research.

### 8.5 Agreement and disagreement with other reviews

Chung et al. conclude in a 2019 literature review (covering literature until 2017) that a recommendation towards an early EVD clamp (i.e. prompt closure) is possible based on the evidence of the RCT by Klopfenstein et al.(7) In this literature search, the only included trial (Klopfenstein) is assessed via pragmatic evaluation and not via validated tools as the Cochrane tool for assessing risk of bias or the GRADE approach.

In an evidence-based consensus statement from the Neurocritical Care Society in 2015 (covering literature until 2014) the authors conclude that the RCT by Klopfenstein et al. demonstrated that rapid weaning can be accomplished safely.(6) The society simultaneously underlines that the recommendation is based upon one RCT with limited number of included patients. The recommendation comprises early EVD discontinuation in order to favor a decreased risk of EVD related infections.

Our review disagrees with the conclusions of these previous reviews in the essence that we do not believe that a recommendation towards a specific weaning strategy is possible based on current available scientific data.

## 9. AUTHORS' CONCLUSIONS

### 9.1 Implications of practice

There is insufficient evidence to favor any of the two investigated strategies for EVD discontinuation in adult patients with external ventricular drainage due to hydrocephalus following aSAH. Current guidelines support prompt closure of the EVD as discontinuation strategy based on the RCT described in this systematic review which has shown to be of very low quality and thus possess deficiencies severe enough to downgrade its level of evidence. Subgroup analyses were not possible to complete due to limited data and this systematic review do not allow for recommendations for clinical practice.

### 9.2 Implications for research

Larger, high-quality, randomized, clinical trials with transparent objective criteria for randomization, pre-published protocols to avoid data-driven reporting bias, independent sequence allocation with proper concealment and description of blinding incl. of outcome assessors are needed to provide reliable prospective data before conclusions regarding benefits and harms of this widely used treatment practice can be drawn safely.



## Acknowledgements

The group of authors would like to thank search coordinator Sarah Klingenberg from Copenhagen Trial Unit for providing the search strategy for this systematic review.

## Contributions of authors

1. Conception or design of the work: TC, ALC, MJ, TM, JW
2. Data collection: TC, ALC, JW
3. Data analysis and interpretation: TC, JW
4. Drafting the article: TC, ALC, JW
5. Critical revision of the article: TC, ALC, MJ, TM, JW
6. Final approval of the version to be published: TC, ALC, MJ, TM, JW

## Declaration of interest

Dr Wetterslev has been a member of the taskforce at Copenhagen Trial Unit to develop theory, manual, and software for doing Trial Sequential Analysis presently freeware at www.ctu.dk/tsa.

## Funding

Dr Capion has received funding from the Research Council at Copenhagen University Hospital Rigshospitalet. The funding party is not involved in the conduct of this review.

## Data sharing statement

Extracted data is available upon reasonable request and only after approval from co-authors and relevant regulatory approvals.

**Figure legends**

Figure 1: *Figure 1: PRISMA flow diagram showing the results of the search*

Figure 2: *Figure 2: Risk of bias assessment. Red = high risk; yellow = unclear risk.*

Figure 3: *Figure 3: Summary of findings table showing the rating of the quality of the evidence for each outcome using the GRADE assessment.*

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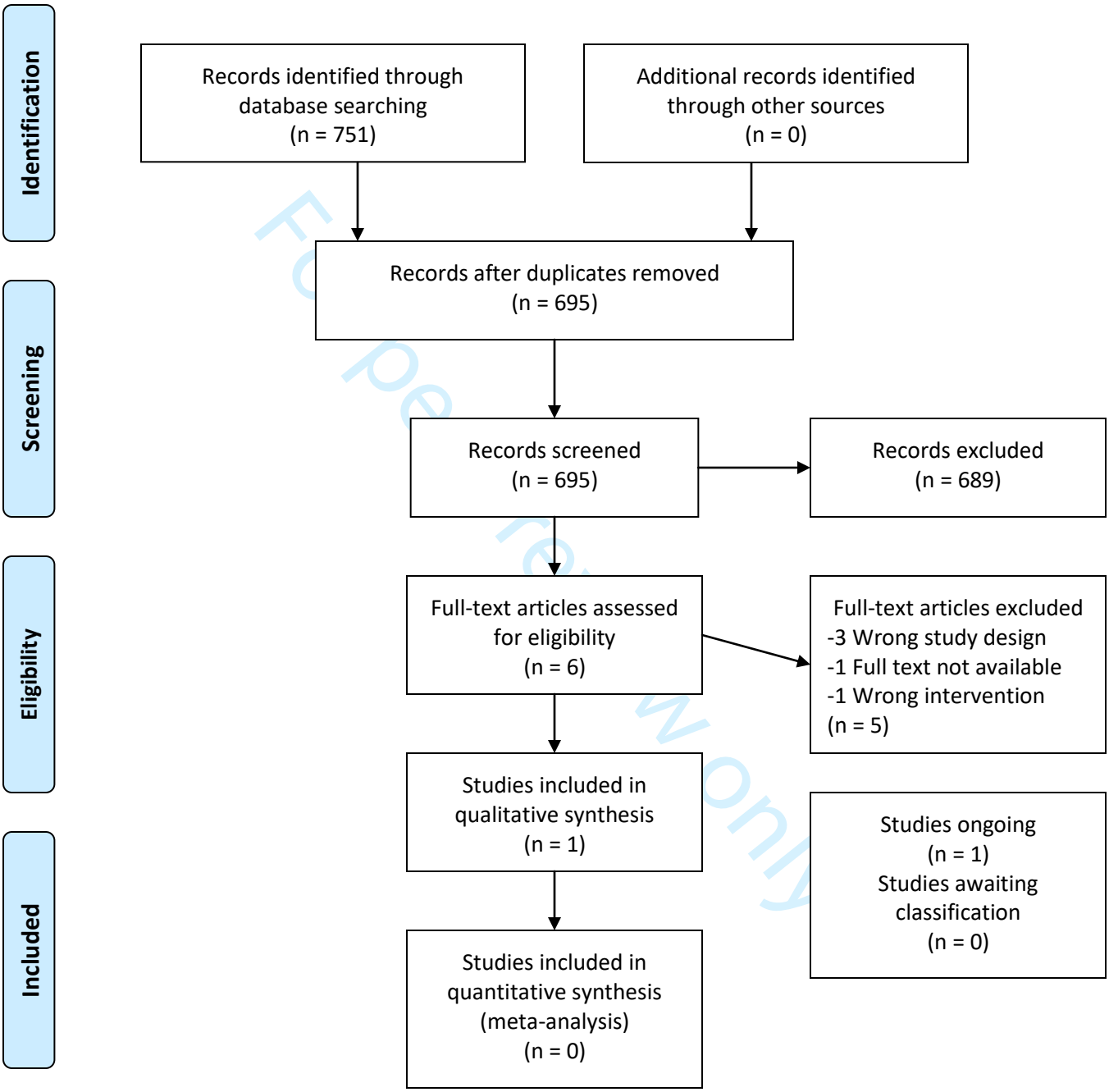
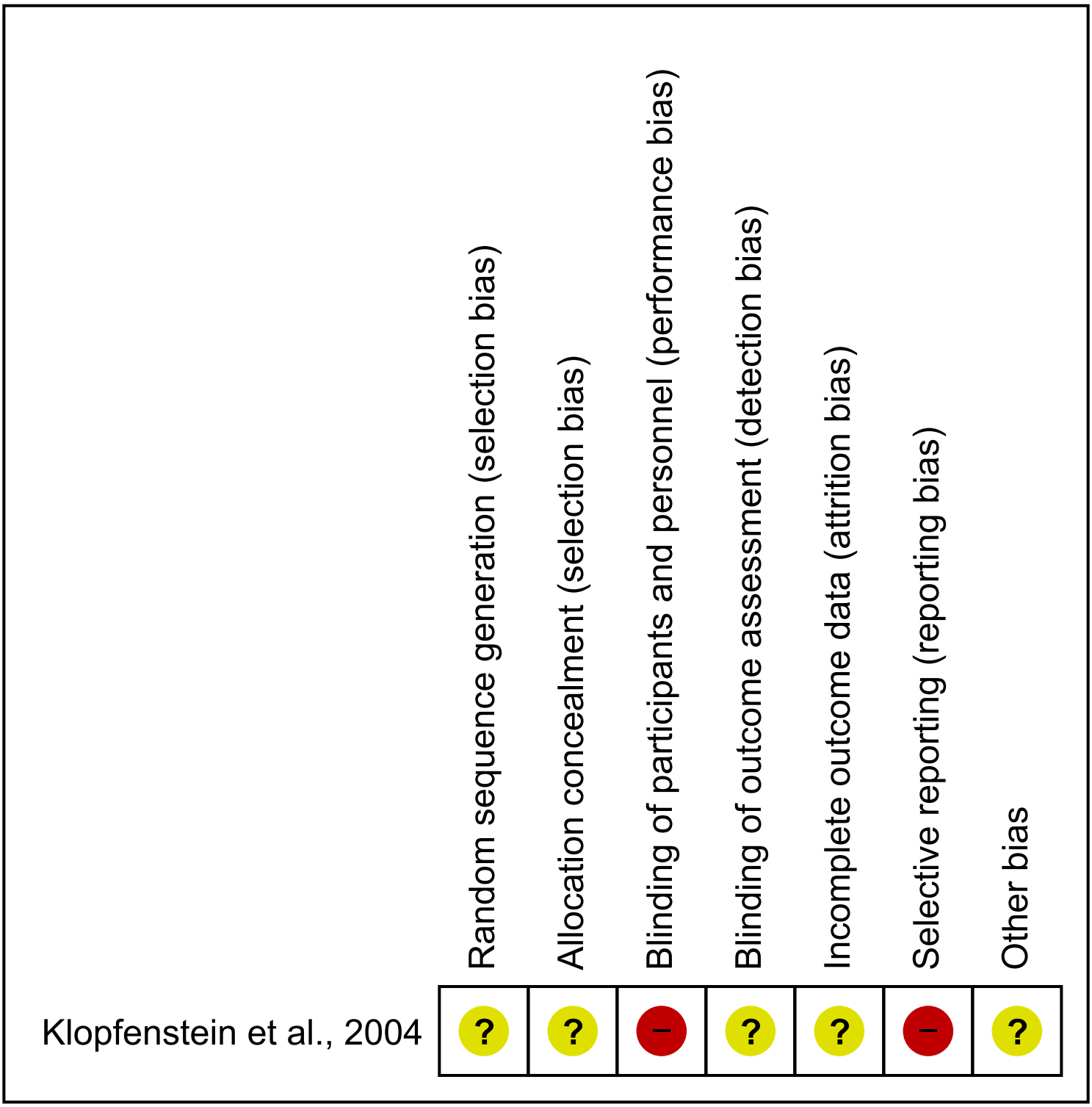
# PRISMA Flow Diagram






*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

**For more information, visit www.prisma-statement.org.**


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Klopfenstein et al., 2004
?
?
–
?
?
–
?

**Summary of findings:**

## Prompt closure compared to gradual weaning in discontinuation of extraventricular drainage

**Patient or population**: discontinuation of extraventricular drainage
**Setting**: hydrocephalus in adult patients following aneurysmal subarachnoid haemorrhage
**Intervention**: prompt closure
**Comparison**: gradual weaning

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | **Risk with gradual weaning** | **Risk with prompt closure** | | | | |
| Death - not reported | - | - | - | - | - | |
| Serious Adverse Events - not reported | - | - | - | - | - | |
| Rate of permanent VP-shunt implementation follow up: mean 7.5 months | 63 per 100 | **63 per 100** (46 to 89) | **RR 1.01** (0.73 to 1.42) | 81 (1 RCT) | ⨁◯◯◯ VERY LOW a,b,c,d,e | The evidence is very uncertain about the effect of prompt closure on rate of permanent VP-shunt implementation. |
| Quality of life - not reported | - | - | - | - | - | |
| Total hospital length of stay (LOS) | The mean total hospital length of stay was **21.5** days | mean **2.4 days lower** (17.1 lower to 12.3 higher) | - | 81 (1 RCT) | ⨁◯◯◯ VERY LOW a,b,c,d,e | Prompt closure may reduce/have little to no effect on total hospital length of stay but the evidence is very uncertain. |
| Total Neuro Intensive Care Unit length of stay (NICU LOS) | The mean total Neuro Intensive Care Unit length of stay was **16.9** days | mean **2.8 days lower** (11.4 lower to 5.8 higher) | - | 81 (1 RCT) | ⨁◯◯◯ VERY LOW a,b,c,d,e | Prompt closure may reduce/have little to no effect on total Neuro Intensive Care Unit length of stay but the evidence is very uncertain. |
| EVD-related complications - not reported | - | - | - | - | - | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

a. Lack of information regarding sequence allocation and concealment of allocation table
b. Lack of blinding
c. Missing description of randomization
d. Very few events
e. Wide confidence intervals

**Search strategies for**
**'Prompt closure vs. gradual weaning of extraventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid hemorrhage'**
**(T Capion)**
**Preliminary searches performed 17 January 2020**

| | |
|---|---|
| **Total number identified** | **1099 records** |
| **Number of duplicates removed** | **367 records** |
| **Number in list** | **732 records** |
| **Number of new records sent to authors** | **84 records** |

**Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2020, Issue 1) (12 hits)**

#1 MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2 (subarachnoid* or SAH)
#3 #1 or #2
#4 MeSH descriptor: [Drainage] explode all trees
#5 MeSH descriptor: [Ventriculostomy] explode all trees
#6 (drain* or ventricul* or evd)
#7 #4 or #5 or #6
#8 MeSH descriptor: [Device Removal] explode all trees
#9 (cessation* or clos* or weaning)
#10 #8 or #9
#11 #3 and #7 and #10

**MEDLINE Ovid (1946 to January 2020) (313 hits)**

1. exp Subarachnoid Hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. exp Drainage/
5. exp Ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 4 or 5 or 6
8. exp Device Removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 8 or 9
11. 3 and 7 and 10

**Embase Ovid (1974 to January 2020) (353 hits)**

1. exp subarachnoid hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. 1 or 2
4. exp drain/
5. exp ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. 4 or 5 or 6
8. exp device removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. 8 or 9
11. 3 and 7 and 10

**LILACS (Bireme; 1982 to January 2020) (4 hits)**
(subarachnoid$ or SAH) [Words] and (drain$ or ventricul$ or evd) [Words] and (cessation$ or clos$ or weaning) [Words]

**Science Citation Index Expanded (1900 to January 2020) and Conference Proceedings Citation Index – Science (1990 to January 2020) (Web of Science) (235 hits)**
#4 #3 AND #2 AND #1
#3 TS=(cessation* or clos* or weaning)
#2 TS=(drain* or ventricul* or evd)
#1 TS=(subarachnoid* or SAH)

**Search strategies for**
**'Prompt closure vs. gradual weaning of extraventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid hemorrhage'**
**(T Capion)**
**Preliminary searches performed 28 November 2018**

| | |
|---|---|
| **Total number identified** | **1033 references** |
| **Number of duplicates removed** | **366 references** |
| **Number in list** | **667 references** |

**Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2018, Issue 11) (6 hits)**

#1 MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2 (subarachnoid* or SAH)
#3 #1 or #2
#4 MeSH descriptor: [Drainage] explode all trees
#5 MeSH descriptor: [Ventriculostomy] explode all trees
#6 (drain* or ventricul* or evd)
#7 #4 or #5 or #6
#8 MeSH descriptor: [Device Removal] explode all trees
#9 (cessation* or clos* or weaning)
#10 #8 or #9
#11 #3 and #7 and #10

**MEDLINE Ovid (1946 to November 2018) (299 hits)**

1. exp Subarachnoid Hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. exp Drainage/
5. exp Ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 4 or 5 or 6
8. exp Device Removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 8 or 9
11. 3 and 7 and 10

**Embase Ovid (1974 to November 2018) (496 hits)**

1. exp subarachnoid hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. 1 or 2
4. exp drain/
5. exp ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. 4 or 5 or 6
8. exp device removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. 8 or 9
11. 3 and 7 and 10

**LILACS (Bireme; 1982 to November 2018) (3 hits)**
(subarachnoid$ or SAH) [Words] and (drain$ or ventricul$ or evd) [Words] and (cessation$ or clos$ or weaning) [Words]

**Science Citation Index Expanded (1900 to November 2018) and Conference Proceedings Citation Index – Science (1990 to November 2018) (Web of Science) (229 hits)**
#4 #3 AND #2 AND #1
#3 TS=(cessation* or clos* or weaning)
#2 TS=(drain* or ventricul* or evd)
#1 TS=(subarachnoid* or SAH)

## Appendix 3: Observational studies

| Study | Objective | Method | Outcomes | Serious Adverse Events |
|---|---|---|---|---|
| Jabbarli R. et al.: *Gradual External Ventricular Drainage Weaning Reduces The Risk of Shunt Dependency After Aneurysmal Subarachnoid Hemorrhage: A Pooled Analysis* | To evaluate the role of external ventricular drainage (EVD) weaning on risk of shunt dependency after SAH | Observational cohort study | Development and timing of shunt dependency in SAH survivals | Shunt dependency: RW: 34.73%, GW: 27.45% (OR 0,71, CI: 0.54-0.94, P = 0,018) |

## Appendix 2: Excluded studies

| | Study # 1 | Study # 2 | Study # 3 | Study # 4 | Study # 5 |
|---|---|---|---|---|---|
| Title | *Csf diversion in aneurysmalsubarachnoid hemorrhage: How low should we go?* | *Gradual External Ventricular Drainage Weaning Reduces The Risk of Shunt Dependency After Aneurysmal Subarachnoid Hemorrhage: a Pooled Analysis* | A comment to: *"Gradual External Ventricular Drainage Weaning Reduces The Risk of Shunt Dependency After Aneurysmal Subarachnoid Hemorrhage: a Pooled Analysis"* | *Continuous cerebral spinal fluid drainage associated with complications in patients admitted with subarachnoid hemorrhage* | *An early EVD clamp trial approach for subarachnoid hemorrhage is associated with a lower ventriculoperitoneal shunt rate, shorter length of stay, and fewer EVD complications-a retrospective study* |
| Authors | Fugate J; Rabenstein A; Wijdicks E; Freeman W; Lanzino G. | Jabbarli R; Pierscianek D; ROlz R; Reinhard M; Darkwah Oppong M; Scheiwe C; Dammann P; Kaier K; Wrede KH; Shah M; Zentner J; Sure U. | Lilja-Cyron A; Mathiesen T. | Olson DM; Zomorodi M; Britz GW; Zomorodi AR; Amato A; Graffagnino C. | Rao S; Wolcott ZC; Chung DY; Sheriff F; Khawaja A; Patel AB; Kimberly WT; Rordorf GA. |
| Year of publication | 2014 | 2018 | 2018 | 2013 | 2017 |
| Journal | Neurology CONFERENCE START: 2014 Apr 26 CONFERENCE END: 2014 May 3 2014;82(10 SUPPL. 1): Lippincott Williams and Wilkins MISC1 - 20140527 2014 | Operative Neurosurgery (hagerstown, md 2018;15(5):498-504 United States NLM (Medline) | Operative neurosurgery 2018;(5):504-504 2018 | Journal of neurosurgery ;119(4):974-980 United States American Association of Neurological Surgeons (1224 West Main Street Suite 450, Charlottesville VA 22903, United States) | Neurocritical care 2017; Conference: 15th Annual Meeting of the Neurocritical Care Society, NCS 2017. United States. 27(2 Supplement 1):S3 Netherlands Humana Press Inc. 2017 |
| Objective | To evaluate the feasibility of | To evaluate the role of external ventricular | Comment to existing article | To explore whether continuous or | To determine the optimal approach of |

| | | | | | |
|---|---|---|---|---|---|
| | randomizing patients with aneurysmal subarachnoid haemorrhage and hydrocephalus to "aggressive" vs "conventional" cerebrospinal drainage | drainage (EVD) weaning on risk of shunt dependency after SAH | | intermittent CSF drainage was superior for reducing vasospasm | gradual wean vs. early clamp trial in nontraumatic SAH requiring EVD |
| Study design | 2-center, prospective, randomized pilot study | Observational cohort study | | Randomized clinical trial | Retrospective study |
| Intervention | Aggressive CSF drainage with EVD open to 5 mmHg vs. conventional CSF drainage with EVD open to 15 mmHg | Rapid weaning vs. gradual weaning of EVD treatment in SAH survivors | | Continuous CSF drainage with intermittent intracranial pressure (ICP) monitoring (open-EVD group) vs. continuous ICP monitoring with intermittent CSF drainage (monitor-ICP group) | Gradual wean vs. early clamp trial in nontraumatic SAH requiring EVD |
| Patients | 20 (13 in the aggressive group) | 965 (455 in the rapid wean group and 510 in the gradual weaning group) | | 60 patients (division between groups unknown) | 200 |
| Outcomes | | Development and timing of shunt dependency | | Incidence of cerebral artery vasospasm | VP shunt rate<br>NICU and hospital LOS<br>EVD duration<br>EVD related infections |
| Reason(s) for exclusion | Wrong intervention<br>Full-text not available | Wrong study design | Wrong study design | Wrong intervention | Wrong study design<br>Full-text not available |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 9 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8-9 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10-11 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 12 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 12-13 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 14 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 15 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | - |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | - |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | - |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 16 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 17 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 18 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19 |



*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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# Prompt closure vs. gradual weaning of external ventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid haemorrhage: A systematic review



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-040722.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 01-Sep-2020 |
| Complete List of Authors: | Capion, Tenna B.; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Lilja-Cyron, Alexander; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Juhler, Marianne; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Mathiesen, Tiit; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Wetterslev , Jørn; Copenhagen University Hospital, Rigshospitalet, Copenhagen Trial Unit; Copenhagen University Hospital, Rigshospitalet, Copenhagen Trial Unit |
| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Intensive care |
| Keywords: | NEUROSURGERY, INTENSIVE & CRITICAL CARE, NEUROLOGY |
| | |

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# Prompt closure vs. gradual weaning of external ventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid haemorrhage: A systematic review

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**Keywords/MeSH terms:** Subarachnoid Hemorrhage/complications, Aneurysm, Hydrocephalus, Treatment outcome

**Word count:** 4593

## 1. ABSTRACT

**Objectives:** To summarize the evidence on benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aneurysmal subarachnoid haemorrhage (aSAH) based on randomized clinical trials in humans.

**Setting:** Randomized, clinical trials (RCT) comparing prompt closure vs. gradual weaning of external ventricular drainage in adult patients with hydrocephalus following aSAH were included.

**Participants:** Patients aged equal to or greater than 18 years with an external ventricular drain (EVD) due to hydrocephalus following aSAH were eligible for inclusion.

**Primary and secondary outcome measures:** Primary outcomes were all-cause mortality, any serious adverse event, rate of ventriculo-peritoneal (VP) shunt placement and quality of life. Secondary outcomes were patients with shunt failure, hospital and Neuro Intensive Care Unit (NICU) length of stay (LOS) and complications related to treatment with an EVD. Data permitted report of rate of VP shunt placement, and hospital and NICU LOS.

**Results:** Six studies were assessed in full-text. One RCT with 81 patients was included. Rate of VP shunt placement was 63.4 % in the rapid weaning group (i.e. prompt closure of the EVD; 41 patients) and 62.5% in the gradual weaning group (40 patients; *p = 0.932*). LOS in hospital and NICU was significantly shorter in the rapidly weaned group compared to the gradually weaned group (mean 19.1 vs. 21.5 days in hospital [*p = 0.03*]; and mean 14.1 vs. 16.9 days in NICU [*p = 0.0002*]). Data was insufficient to conduct meta-analysis, trial sequential analysis or subgroup analysis of heterogeneity and sensitivity. One RCT is currently ongoing.

**Conclusions:** We found insufficient evidence to favor any of the two strategies for EVD discontinuation in patients with hydrocephalus following aSAH.

**Trial registration:** This systematic review was preceded by a published protocol and is registered in the PROSPERO register under the ID number CRD42018108801

## 2. ARTICLESUMMARY

Strengths and limitations of this study

Strengths

1) Patient centered outcomes
2) Rigorous assessment of bias and the risk of random errors
3) GRADE assessment of the quality of the total evidence

Limitations

1) One included RCT
2) Recommendations from systematic reviews may suffer from the quality of the included trials

## 3. BACKGROUND

Aneurysmal SAH (aSAH) is a common and often devastating cerebrovascular disease accounting for approximately 7 % of all strokes.(1) Acute hydrocephalus due to blockage of cerebrospinal fluid (CSF) circulation occurs as a common and severe complication, which is treated with an external ventricular drain (EVD) in the acute phase. An EVD enables removal of CSF and subsequently management of intracranial pressure (ICP).(2,3) Up to 37 % of patients with an EVD develop chronic hydrocephalus during the course of the disease, requiring permanent diversion of CSF via a ventriculo-peritoneal (VP) shunt.(2) How to increase safety of EVD discontinuation and reduce the need for a VP-shunt is debated. Two different strategies are typically being used to assess for dependence of drainage; prompt closure or gradual weaning of the EVD. The latter is performed by stepwise increase of drainage resistance to outflow over days. It is unknown whether these two strategies result in differentiated clinical outcomes, different risks for VP shunt placement or whether they lead to different complication rates of EVD and VP-shunt treatment.

### 3.1 Description of the condition

In adults, CSF production is constant at approximately 500 ml/day. Thus CSF circulation and absorption occur at a similar rate keeping the system in balance. Post-haemorrhagic hypersecretion of CSF or obstruction of CSF circulation and absorption result in hydrocephalus.(4) The reported prevalence of hydrocephalus following aSAH ranges between 6 % and 67 %, and three stages of hydrocephalus are generally recognized: acute (0-3 days after SAH), subacute (4-13 days after SAH) and chronic ($\geq$ 14 days after SAH).(3)

### 3.2 Description of the intervention

Scientific data to define timing and choice of strategy for discontinuation and removal of an EVD inserted to treat hydrocephalus following aSAH is sparse. In some patients circulation of CSF returns to normal within days or weeks, permitting the EVD to be removed with ICP within normal range and no further need for treatment. In other patients, chronic hydrocephalus evolves with the need for an implanted permanent drainage solution (a VP shunt)(5) which diverts CSF from the brain ventricles to the abdomen where it is absorbed. Prolonged duration of EVD treatment as seen in gradual weaning of the EVD is an attempt to await potential return of normal CSF circulation and thereby avoid a permanent shunt. However, the risk of serious and potentially fatal infection (ventriculitis, meningitis, cerebral abscess) increases with prolonged EVD treatment. Conversely, early discontinuation may involve risks associated with increased ICP and acute hydrocephalus and possibly increased risk for placement of a permanent shunt.

### 3.3 How the intervention might work

The process of identifying patients who will need a permanent VP shunt involves a trial of closure of the EVD. The main argument in favour of prompt closure of the EVD is to minimize the treatment period and thereby the risk of infection. Subsequently, patients could potentially be discharged earlier from the hospital and thus begin rehabilitation sooner. The arguments in favour of weaning by gradually increasing drainage resistance involves time for reestablishment of normal CSF circulation, and thus less drastic changes in ICP with potential protection of brain tissue.

### 3.4 Why it is important to do this review

A possible difference between the two treatment strategies is important to identify as difference in treatment may affect patient outcomes. Insertion of a VP shunt is best defined as a surrogate outcome measure in the present context, as the indication for the procedure seems to vary throughout and the procedure is associated with risks for the patient (i.e. mechanical shunt dysfunction and shunt related infections) and increased medical costs for society as shunt complications frequently require additional hospitalizations and surgical interventions.

Previous reviews within this field have compared the two EVD discontinuation strategies in patients with hydrocephalus following aSAH via comprehensive literature searches without pre-published protocols or pre-defined hypotheses or data extraction plans, and without a validated rating of the available evidence.(6,7) A review that methodologically meets the rigorous demands for systematic reviews as

defined by the PRISMA guidelines (and 2015 PRISMA-P statement) provides the highest possible impact for researchers to use in forthcoming work and investigation of this medical issue.(8)

## 4. OBJECTIVES

To summarize the evidence on benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH based on randomized clinical trials in humans.

## 5. METHODS

### 5.1 Criteria for considering studies for this review

#### 5.1.1 Types of studies

This systematic review was conducted in accordance with PROSPERO registration (CRD42018108801) and a pre-published protocol.(9) The recommendations from the Cochrane Collaboration, the PRISMA guidelines for systematic reviews (8) and the GRADE assessment were followed.(10)

Randomized clinical trials (RCT) comparing prompt closure vs. gradual weaning of external ventricular drainage in patients with aSAH were included in qualitative evaluations of intervention effects in this systematic review. Additionally, observational studies were included in an appendix enumerating findings of serious adverse events (SAE).

Studies were assessed without consideration of publication status, blinding status or language. No unpublished trials or trials using quasi-randomization were included.

#### 5.1.2 Types of participants

Patients aged equal to or greater than 18 years with an EVD due to hydrocephalus following aSAH were eligible for inclusion.

#### 5.1.3 Types of interventions

Interventions studied involve prompt closure, i.e. the direct closure of the EVD, vs. gradual weaning, i.e. a gradual increase of resistance to outflow over days, of external ventricular drainage due to hydrocephalus following aSAH.

#### 5.1.4 Types of outcome measures

Predefined primary outcomes include death from any cause, any SAE defined according to the International Conference of Harmonization of Good Clinical Practice (ICH-GCP)(11), complications and adverse events

specific for EVD and VP shunt systems (clinical and radiological signs of shunt obstruction, and clinical and microbiological signs of ventriculitis and shunt infection), rate of permanent VP shunt placement and quality of life measured (QoL) with any score.

Predefined secondary outcomes comprise number of shunt interventions following the primary shunt insertion (surgical shunt interventions for any reason) within the longest follow-up in each trial, total hospital and NICU length of stay (LOS), and EVD related complications (ventriculitis defined as positive CSF culture, clinically relevant intracranial haemorrhage requiring surgical evacuation or additional surgical procedure secondary to EVD misplacement).

### 5.2 Search methods for identification of studies

#### 5.2.1 Electronic searches

Searches were performed without language or date restrictions. The following electronic databases were searched: The Cochrane Library's Central Register of Controlled trials (CENTRAL), MEDLINE (1946 to date) (Ovid SP), EMBASE (1974 to date) (Ovid SP), LILACS (1982 to date) (BIREME), Science Citation Index Expanded (1900 to November 2018) and Conference Proceedings Citation Index – Science (1990 to November 2018) (Web of Science). The preliminary search was performed on November 28th 2018 and repeated on January 20th 2020. The search strategies can be seen in Appendix 1.

#### 5.2.2 Searching other resources

Studies included in the full text screening were hand searched for supplemental studies not registered in the electronic searches. Main authors of studies were contacted for any missed, unreported or ongoing trials and to retrieve relevant data.

### 5.3 Data collection and analysis

Main authors of studies included in the trial were contacted in case their publication did not contain sufficient information for risk of bias assessment and data extraction of our chosen outcomes.

#### 5.3.1 Selection of studies

Two review authors (TC and ALC) independently evaluated all relevant references and provided a detailed description of included and excluded trials.

#### 5.3.2 Data extraction and management

Titles and abstracts were screened in order to identify studies that were eligible. TC and ALC independently extracted and collected data using the Covidence software (*Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia*). We were not blinded to the author, institution or the publication source of trials. Disagreements were resolved by JW.

Review Manager Software (*Review Manager (RevMan) [Computer program], version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014*) was used as statistical software.

### 5.3.3 Assessment of risk of bias in included studies

TC and ALC independently conducted the assessment of risk of bias using The Cochrane Collaboration's recommended tool for assessing risk of bias. Disagreements were resolved by JW.

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. 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 of the quality of evidence for the results of each outcome.(12)

### 5.3.4 Dealing with missing data

Main authors of included trials were contacted in order to retrieve missing data.

For further details about the handling of missing data, and for details regarding assessment of heterogeneity, reporting bias, data synthesis, meta-analysis, trial sequential analysis, and subgroup and sensitivity analysis, please see published review protocol.(9)

### 5.3.5 GRADE

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate and assess the quality of the evidence for each outcome.(10) A summary of findings table was produced summarizing the quality of evidence for each outcome.

## 6. R E S U L T S

### 6.1 Description of studies

### 6.1.1 Results of the search

We identified 751 references via a primary search in November 2018 and an updated search in January 2020. Fifty-six references were removed as duplicates, leaving 695 to be screened for title and abstract. Of these, 6 studies were assessed in full-text. We found one RCT which met the inclusion criteria(13) (figure 1) and one observational study to be included in appendix(14) (appendix 2). No studies describing prompt closure vs. gradual weaning of external ventricular drainage in other conditions such as spontaneous intracranial hemorrhage were found.

### 6.1.2 Included studies

The included RCT by Klopfenstein et al. from 2004 (13) randomized 81 adult patients with hydrocephalus following aSAH to either rapid or gradual weaning of the EVD. A rapid wean signified prompt closure of the EVD at time of intervention, whereas gradual weaning comprised four steps of increasing drainage resistance to outflow ending at complete closure of the EVD. Of the 81 randomized patients, 41 were in the rapidly weaned group and 40 patients were in the gradually weaned group. The primary outcome of this trial was rate of VP shunt placement. Secondary outcomes were i) number of days in which the EVD was in place; ii) number of days the patient spent in the ICU; and iii) overall duration of hospital stay.
All patients who failed either form of EVD discontinuation underwent shunt placement, resulting in equal shunt rates for the two groups. In the gradually weaned group the EVD remained in place for significantly longer time, while LOS in hospital and NICU were significantly longer for the gradually weaned group. No data were available for death by any cause, SAE or QoL at longest follow-up.
The authors concluded that gradual weaning provides no advantage over prompt closure in terms of rate of VP shunt placement, and that prompt closure should as such be pursued in the treatment of patients with aSAH due to shorter LOS in hospital and NICU and shorter time with EVD in place.
Contact by email to the corresponding and last author of this study in order to retrieve additional relevant data was attempted without result.

One observational cohort study comparing prompt closure vs. gradual weaning of EVD treatment in patients with aSAH was included in an appendix enumerating adverse effects (Appendix 2).(14) The study by Jabbarli et al. from 2018 compared treatment effects in two individual German institutions using different discontinuation strategies for external ventricular drainage in patients with aSAH. Outcomes were development and timing of shunt dependency. The authors concluded that patients treated by rapid weaning (i.e. prompt closure) of the EVD had significantly higher risk of getting a VP shunt and that gradual weaning led to longer EVD treatment but not in the expense of higher risk of drain related infections.

Contact by email to the corresponding author of this study in order to retrieve additional relevant data was attempted without result.

### 6.1.3 Excluded studies

Of the six studies included in the full-text screening, five studies were excluded.

One study was excluded due to wrong study intervention. The randomized, clinical trial by Olson et al. from 2013 compared continuous vs. intermittent external ventricular drainage in patients with an EVD due to hydrocephalus following aSAH. The study was terminated after the inclusion of 60 patients due to a higher complication rate in the continuous drainage group.(15)

Two of the excluded studies were conference papers to which full-texts were not available. In one of these studies, authors carried out a prospective, randomized pilot study to determine the feasibility of randomizing patients with an EVD after aSAH to either aggressive or conventional external ventricular drainage. The authors included 20 patients of which 13 were in the aggressive arm, and concluded that randomization is possible. The corresponding author to this study has via email informed that completion of the article was not pursued, nor was further progression with an RCT.

The second study was an abstract of a retrospective assessment of 200 patients with an EVD due to non-traumatic (aneurysmal) SAH(16) comparing gradual wean and early clamp trial of the EVD. The authors compared rate of VP shunt placement, NICU and hospital LOS, EVD duration and rate of EVD related infections and concluded that an early clamp trial was associated with fewer complications and shorter LOS compared to gradual weaning.

The last two references were excluded due to wrong study design; one was an observational study(14) carried out in 2018 which evaluated the role of EVD weaning on rate of VP shunt placement in 965 patients with aSAH. The authors concluded that at the expense of longer treatment, gradual EVD weaning may decrease the risk of shunt dependency without an additional risk of CSF infection. The second reference omitted due to wrong study design was a comment to the study by Jabbarli et al.(14), featured in the end of the article as contribution.

Details of the 5 excluded studies can be seen in appendix 3.

### 6.2 Risk of bias in included studies

Using the Cochrane Collaboration's tool for assessing risk of bias we found that the included study had limitations in design and execution severe enough to downgrade the quality of evidence. No information regarding allocation table or concealment was provided which resulted in unclear risk of selection bias.

Participants and personnel were not blinded to the intervention due to the nature of the intervention. Patients were randomized at time of enrollment. The timing of intervention was decided by a treating physician not involved in the trial execution but blinded to the outcome of the randomization. No details describing how the randomization process was performed were provided. We assessed the risk of performance bias and detection bias as high.

Outcome was reported for the 51 patients out of 81 who received a VP shunt. Follow-up status for the remaining 30 patients was not reported. Intent-to-treat analysis was described for the primary outcome but not for secondary outcomes. The numbers of eligible, included and excluded patients were provided. The reasons for patient exclusion and withdrawal were not specified, neither was information about the handling of the excluded patients in terms of randomization or intention-to-treat analysis. The risk of attrition bias was due to these limitations assessed as unclear. Further, patient-centered outcomes such as mortality, number of SAE, complications related to EVD and VP shunt treatment and QoL were not reported which made risk of reporting bias high. No study protocol was published before the study paper and no sample size calculations were provided which might have led to data driven reporting bias.

These limitations are severe in their generation of the overall risk of bias as they might individually and combined cause bias to the execution of the study and to the randomization process which may cause systematic bias in the inclusion and division of patients and thus to the results of the study. Based on the assessed domains the overall risk of bias of the included study was assessed as high (figure 2).

### 6.3 Effects of interventions

The only primary outcome for which the included RCT provided data was rate of VP shunt placement. All patients who failed either form of EVD discontinuation underwent shunt placement, resulting in a shunt rate of 63.4 % and 62.5 % for rapid or gradual wean, respectively ($p = 0.932$). Certainty for this outcome assessed via the GRADE approach was considered very low primarily due to very serious risk of bias, very serious imprecision and serious indirectness.

Secondary outcomes for which data were available were time with EVD in place, and hospital and NICU LOS. In the rapidly weaned group the EVD remained in place for significantly shorter time compared to the gradually weaned group (mean of 12.7 vs. 15.8 days, $p = 0.000009$). LOS in hospital and NICU was also shorter for the rapidly weaned group (19.1 vs. 21.5 days in hospital [$p = 0.03$]; 14.1 vs. 16.9 days in NICU [$p = 0.0002$]). The certainty for these outcomes was equally considered very low based on very serious risk of bias, very serious imprecision and serious indirectness.

The power of the included RCT (81 patients) does not reach required information size (RIS) to conduct a reliable and conclusive meta-analysis which in size is expected to be at least that of the sample size of one

well-powered RCT for a reliable detection or rejection of an anticipated intervention effect.(17) A study with few patients and few events, and thus wide confidence intervals, raises imprecision and uncertainty about the results, as is also the result in the present included RCT.

### 6.4 Patient and public involvement

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

### 6.5 Ethics and dissemination

The evidence on the benefits and harms of the two common strategies for EVD discontinuation in patients with hydrocephalus following aSAH is sparse, and no methodologically thorough systematic review has been conducted until this point. Results from this review will be published internationally according to the interest of the society. No possible impact, harm or ethical concerns are expected due to this review.

The protocol for this systematic review was published before the conduction of the review which makes it possible for other peer reviewers and editors to be able to measure the completeness and transparency of this systematic review.

## 7. DISCUSSION

This systematic review aimed at assessing the evidence of benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH. We conducted an extensive literature search which resulted in just 6 studies evaluated in full text. We included one RCT with 81 patients which concluded that prompt closure is safe and reduce LOS in hospital and NICU. We assessed however the RCT by Klopfenstein et al. to be of overall low quality with high risk of bias and thus insufficient in order to provide high-quality evidence to support or refute either of the two investigated strategies for EVD discontinuation. Despite the assessed quality of the RCT, the current international guidelines covering this issue base their recommendations solely on the results from this study.(18) Previous reviews differ in design and methodology, they do not assess the quality of included studies in detail, and they support the recommendations for prompt closure as discontinuation strategy despite the above mentioned shortages in evidence.(6,7) There is currently no high-quality evidence to cover this information gap.

The present systematic review is the first of its kind to address the question of EVD discontinuation strategy after aSAH by assessment of included studies using the Cochrane risk of bias tool and the GRADE approach,

and it disagrees with previous review conclusions on the applicability of the results of the included RCT in international recommendations and guidelines.

### 7.1 Summary of main results

One RCT with 81 patients was included in this systematic review. The included trial showed very serious risk of bias and imprecision and an overall very low quality assessment based on the GRADE approach and the Cochrane risk of bias tool. Required information size to provide reliable meta-analysis and TSA on our chosen outcomes was not reached and it was impossible to conduct subgroup and sensitivity analyses to investigate reasons for heterogeneity.

### 7.2 Overall completeness and applicability of evidence

There is insufficient evidence to favor any of the two investigated strategies for discontinuation of external ventricular drainage in patients with hydrocephalus following aSAH.

### 7.3 Quality of the evidence

Based on GRADE the certainty of the evidence for the primary outcome and the two secondary outcomes, for which data was provided, was in all cases assessed as 'very low'. These assessments were mainly based on very serious risk of bias, very serious imprecision and serious indirectness (figure 3).

For the remaining 3 primary outcomes and 2 secondary outcomes which this systematic review sought to evaluate there were no available data.

### 7.4 Potential biases in the review process

The authors to this review has based on the preliminary literature search in November 2018 initiated and launched an RCT comparing prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH which is currently ongoing. We might as such be biased in assessing methods within this field as we have previously done extensive literature search within this area of research.

### 7.5 Agreement and disagreement with other reviews

Chung et al. conclude in a 2019 literature review (covering literature until 2017) that a recommendation towards an early EVD clamp (i.e. prompt closure) is possible based on the evidence of the RCT by Klopfenstein et al.(7) In this literature search, the only included trial (Klopfenstein) is assessed via pragmatic

evaluation and not via validated tools as the Cochrane tool for assessing risk of bias or the GRADE approach.

In an evidence-based consensus statement from the Neurocritical Care Society in 2015 (covering literature until 2014) the authors conclude that the RCT by Klopfenstein et al. demonstrated that rapid weaning can be accomplished safely.(6) The society simultaneously underlines that the recommendation is based upon one RCT with limited number of included patients. The recommendation comprises early EVD discontinuation in order to favor a decreased risk of EVD related infections.

Our review disagrees with the conclusions of these previous reviews in the essence that we do not believe that a recommendation towards a specific weaning strategy is possible based on current available scientific data.

## 8. AUTHORS' CONCLUSIONS

### 8.1 Implications of practice

There is insufficient evidence to favor any of the two investigated strategies for EVD discontinuation in adult patients with external ventricular drainage due to hydrocephalus following aSAH. Current guidelines support prompt closure of the EVD as discontinuation strategy based on the RCT described in this systematic review which has shown to be of very low quality and thus possess deficiencies severe enough to downgrade its level of evidence. Subgroup analyses were not possible to complete due to limited data and this systematic review do not allow for recommendations for clinical practice.

### 8.2 Implications for research

Larger, high-quality, randomized, clinical trials with transparent objective criteria for randomization, pre-published protocols to avoid data-driven reporting bias, independent sequence allocation with proper concealment and description of blinding incl. of outcome assessors are needed to provide reliable prospective data before conclusions regarding benefits and harms of this widely used treatment practice can be drawn safely.

## Acknowledgements

The group of authors would like to thank search coordinator Sarah Klingenberg from Copenhagen Trial Unit for providing the search strategy for this systematic review.

## Contributions of authors

1. Conception or design of the work: TC, ALC, MJ, TM, JW

2. Data collection: TC, ALC, JW
3. Data analysis and interpretation: TC, JW
4. Drafting the article: TC, ALC, JW
5. Critical revision of the article: TC, ALC, MJ, TM, JW
6. Final approval of the version to be published: TC, ALC, MJ, TM, JW

## Declaration of interest

Dr Wetterslev has been a member of the taskforce at Copenhagen Trial Unit to develop theory, manual, and software for doing Trial Sequential Analysis presently freeware at www.ctu.dk/tsa.

## Funding

Dr Capion has received funding from the Research Council at Copenhagen University Hospital Rigshospitalet (Grant no. E-23565-03). The funding party is not involved in the conduct of this review.

## Data sharing statement

Extracted data is available upon reasonable request and only after approval from co-authors and relevant regulatory approvals.

### Figure legends

Figure 1: *Figure 1: PRISMA flow diagram showing the results of the search*

Figure 2: *Figure 2: Risk of bias assessment. Red = high risk; yellow = unclear risk.*

Figure 3: *Figure 3: Summary of findings table showing the rating of the quality of the evidence for each outcome using the GRADE assessment.*

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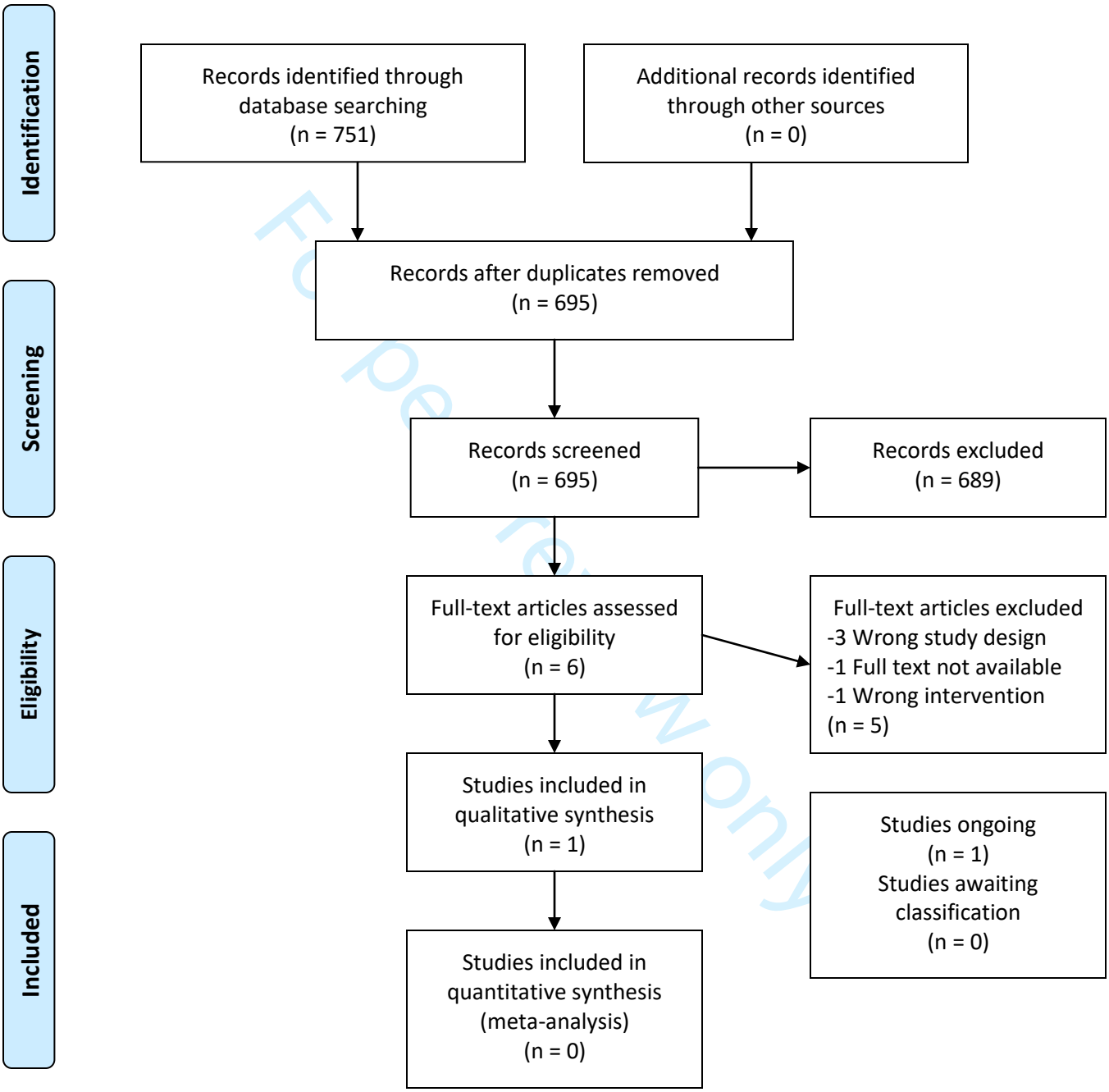
## PRISMA Flow Diagram






*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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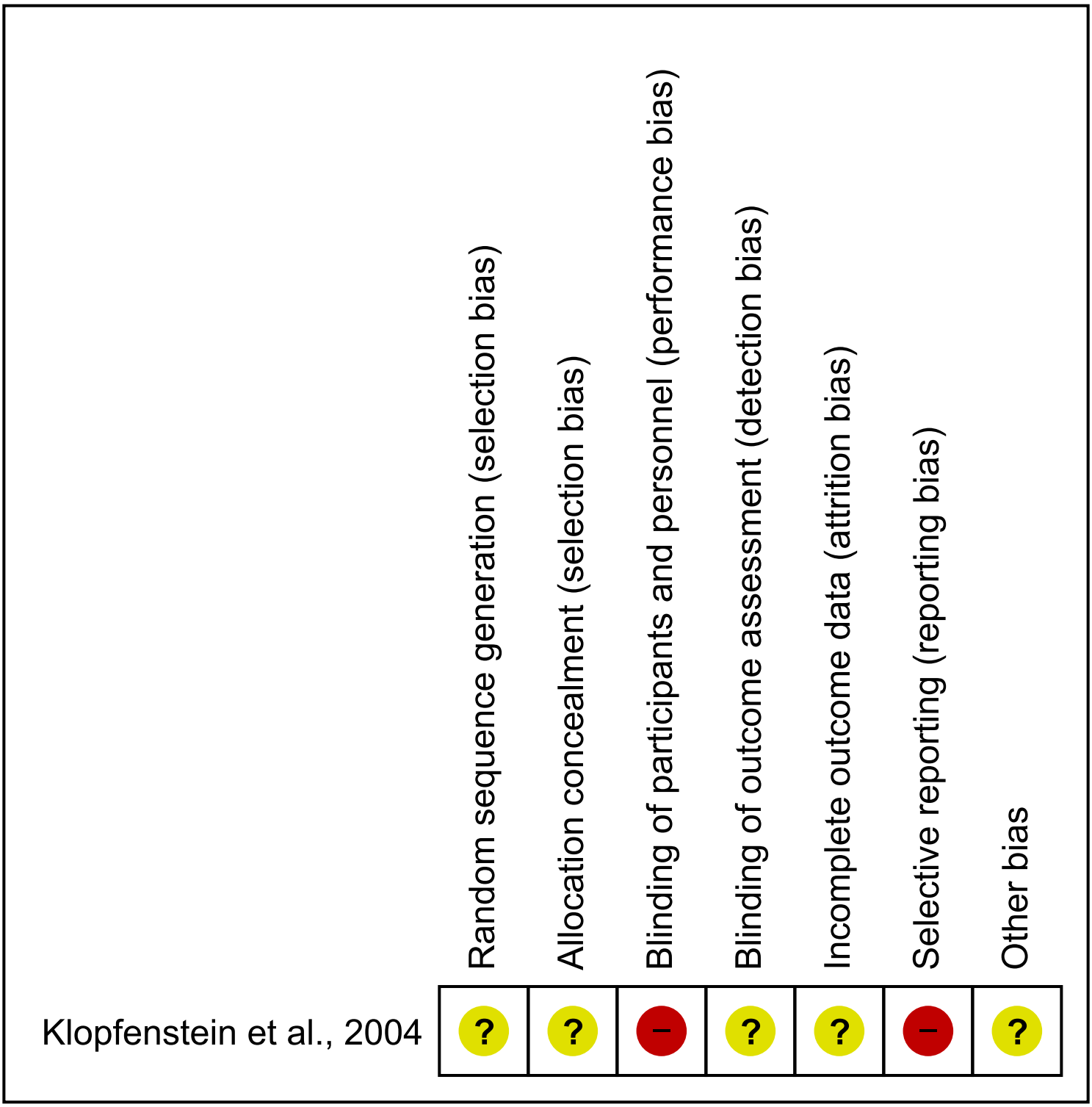
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Klopfenstein et al., 2004
?
?
–
?
?
–
?

**Summary of findings:**

## Prompt closure compared to gradual weaning in discontinuation of extraventricular drainage

**Patient or population**: discontinuation of extraventricular drainage
**Setting**: hydrocephalus in adult patients following aneurysmal subarachnoid haemorrhage
**Intervention**: prompt closure
**Comparison**: gradual weaning

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | **Risk with gradual weaning** | **Risk with prompt closure** | | | | |
| Death - not reported | - | - | - | - | - | |
| Serious Adverse Events - not reported | - | - | - | - | - | |
| Rate of permanent VP-shunt implementation follow up: mean 7.5 months | 63 per 100 | **63 per 100** (46 to 89) | **RR 1.01** (0.73 to 1.42) | 81 (1 RCT) | ⨁◯◯◯ VERY LOW a,b,c,d,e | The evidence is very uncertain about the effect of prompt closure on rate of permanent VP-shunt implementation. |
| Quality of life - not reported | - | - | - | - | - | |
| Total hospital length of stay (LOS) | The mean total hospital length of stay was **21.5** days | mean **2.4 days lower** (17.1 lower to 12.3 higher) | - | 81 (1 RCT) | ⨁◯◯◯ VERY LOW a,b,c,d,e | Prompt closure may reduce/have little to no effect on total hospital length of stay but the evidence is very uncertain. |
| Total Neuro Intensive Care Unit length of stay (NICU LOS) | The mean total Neuro Intensive Care Unit length of stay was **16.9** days | mean **2.8 days lower** (11.4 lower to 5.8 higher) | - | 81 (1 RCT) | ⨁◯◯◯ VERY LOW a,b,c,d,e | Prompt closure may reduce/have little to no effect on total Neuro Intensive Care Unit length of stay but the evidence is very uncertain. |
| EVD-related complications - not reported | - | - | - | - | - | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

a. Lack of information regarding sequence allocation and concealment of allocation table
b. Lack of blinding
c. Missing description of randomization
d. Very few events
e. Wide confidence intervals

**Search strategies for**
**'Prompt closure vs. gradual weaning of extraventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid hemorrhage'**
**(T Capion)**
**Preliminary searches performed 17 January 2020**

| | |
|---|---|
| **Total number identified** | **1099 records** |
| **Number of duplicates removed** | **367 records** |
| **Number in list** | **732 records** |
| **Number of new records sent to authors** | **84 records** |

**Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2020, Issue 1) (12 hits)**

#1 MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2 (subarachnoid* or SAH)
#3 #1 or #2
#4 MeSH descriptor: [Drainage] explode all trees
#5 MeSH descriptor: [Ventriculostomy] explode all trees
#6 (drain* or ventricul* or evd)
#7 #4 or #5 or #6
#8 MeSH descriptor: [Device Removal] explode all trees
#9 (cessation* or clos* or weaning)
#10 #8 or #9
#11 #3 and #7 and #10

**MEDLINE Ovid (1946 to January 2020) (313 hits)**

1. exp Subarachnoid Hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. exp Drainage/
5. exp Ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 4 or 5 or 6
8. exp Device Removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 8 or 9
11. 3 and 7 and 10

**Embase Ovid (1974 to January 2020) (353 hits)**

1. exp subarachnoid hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. 1 or 2
4. exp drain/
5. exp ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. 4 or 5 or 6
8. exp device removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. 8 or 9
11. 3 and 7 and 10

**LILACS (Bireme; 1982 to January 2020) (4 hits)**
(subarachnoid$ or SAH) [Words] and (drain$ or ventricul$ or evd) [Words] and (cessation$ or clos$ or weaning) [Words]

**Science Citation Index Expanded (1900 to January 2020) and Conference Proceedings Citation Index – Science (1990 to January 2020) (Web of Science) (235 hits)**
#4 #3 AND #2 AND #1
#3 TS=(cessation* or clos* or weaning)
#2 TS=(drain* or ventricul* or evd)
#1 TS=(subarachnoid* or SAH)

**Search strategies for**
**'Prompt closure vs. gradual weaning of extraventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid hemorrhage'**
**(T Capion)**
**Preliminary searches performed 28 November 2018**

| | |
|---|---|
| **Total number identified** | **1033 references** |
| **Number of duplicates removed** | **366 references** |
| **Number in list** | **667 references** |

**Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2018, Issue 11) (6 hits)**

#1 MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2 (subarachnoid* or SAH)
#3 #1 or #2
#4 MeSH descriptor: [Drainage] explode all trees
#5 MeSH descriptor: [Ventriculostomy] explode all trees
#6 (drain* or ventricul* or evd)
#7 #4 or #5 or #6
#8 MeSH descriptor: [Device Removal] explode all trees
#9 (cessation* or clos* or weaning)
#10 #8 or #9
#11 #3 and #7 and #10

**MEDLINE Ovid (1946 to November 2018) (299 hits)**

1. exp Subarachnoid Hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. exp Drainage/
5. exp Ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 4 or 5 or 6
8. exp Device Removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 8 or 9
11. 3 and 7 and 10

**Embase Ovid (1974 to November 2018) (496 hits)**

1. exp subarachnoid hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. 1 or 2
4. exp drain/
5. exp ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. 4 or 5 or 6
8. exp device removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. 8 or 9
11. 3 and 7 and 10

**LILACS (Bireme; 1982 to November 2018) (3 hits)**
(subarachnoid$ or SAH) [Words] and (drain$ or ventricul$ or evd) [Words] and (cessation$ or clos$ or weaning) [Words]

**Science Citation Index Expanded (1900 to November 2018) and Conference Proceedings Citation Index – Science (1990 to November 2018) (Web of Science) (229 hits)**
#4 #3 AND #2 AND #1
#3 TS=(cessation* or clos* or weaning)
#2 TS=(drain* or ventricul* or evd)
#1 TS=(subarachnoid* or SAH)

## Appendix 3: Observational studies

| Study | Objective | Method | Outcomes | Serious Adverse Events |
|---|---|---|---|---|
| Jabbarli R. et al.: *Gradual External Ventricular Drainage Weaning Reduces The Risk of Shunt Dependency After Aneurysmal Subarachnoid Hemorrhage: A Pooled Analysis* | To evaluate the role of external ventricular drainage (EVD) weaning on risk of shunt dependency after SAH | Observational cohort study | Development and timing of shunt dependency in SAH survivals | Shunt dependency: RW: 34.73%, GW: 27.45% (OR 0,71, CI: 0.54-0.94, P = 0,018) |

## Appendix 2: Excluded studies

| | Study # 1 | Study # 2 | Study # 3 | Study # 4 | Study # 5 |
|---|---|---|---|---|---|
| Title | *Csf diversion in aneurysmalsubarachnoid hemorrhage: How low should we go?* | *Gradual External Ventricular Drainage Weaning Reduces The Risk of Shunt Dependency After Aneurysmal Subarachnoid Hemorrhage: a Pooled Analysis* | A comment to: *"Gradual External Ventricular Drainage Weaning Reduces The Risk of Shunt Dependency After Aneurysmal Subarachnoid Hemorrhage: a Pooled Analysis"* | *Continuous cerebral spinal fluid drainage associated with complications in patients admitted with subarachnoid hemorrhage* | *An early EVD clamp trial approach for subarachnoid hemorrhage is associated with a lower ventriculoperitoneal shunt rate, shorter length of stay, and fewer EVD complications-a retrospective study* |
| Authors | Fugate J; Rabenstein A; Wijdicks E; Freeman W; Lanzino G. | Jabbarli R; Pierscianek D; ROlz R; Reinhard M; Darkwah Oppong M; Scheiwe C; Dammann P; Kaier K; Wrede KH; Shah M; Zentner J; Sure U. | Lilja-Cyron A; Mathiesen T. | Olson DM; Zomorodi M; Britz GW; Zomorodi AR; Amato A; Graffagnino C. | Rao S; Wolcott ZC; Chung DY; Sheriff F; Khawaja A; Patel AB; Kimberly WT; Rordorf GA. |
| Year of publication | 2014 | 2018 | 2018 | 2013 | 2017 |
| Journal | Neurology CONFERENCE START: 2014 Apr 26 CONFERENCE END: 2014 May 3 2014;82(10 SUPPL. 1): Lippincott Williams and Wilkins MISC1 - 20140527 2014 | Operative Neurosurgery (hagerstown, md 2018;15(5):498-504 United States NLM (Medline) | Operative neurosurgery 2018;(5):504-504 2018 | Journal of neurosurgery ;119(4):974-980 United States American Association of Neurological Surgeons (1224 West Main Street Suite 450, Charlottesville VA 22903, United States) | Neurocritical care 2017; Conference: 15th Annual Meeting of the Neurocritical Care Society, NCS 2017. United States. 27(2 Supplement 1):S3 Netherlands Humana Press Inc. 2017 |
| Objective | To evaluate the feasibility of | To evaluate the role of external ventricular | Comment to existing article | To explore whether continuous or | To determine the optimal approach of |

| | | | | | |
|---|---|---|---|---|---|
| | randomizing patients with aneurysmal subarachnoid haemorrhage and hydrocephalus to "aggressive" vs "conventional" cerebrospinal drainage | drainage (EVD) weaning on risk of shunt dependency after SAH | | intermittent CSF drainage was superior for reducing vasospasm | gradual wean vs. early clamp trial in nontraumatic SAH requiring EVD |
| Study design | 2-center, prospective, randomized pilot study | Observational cohort study | | Randomized clinical trial | Retrospective study |
| Intervention | Aggressive CSF drainage with EVD open to 5 mmHg vs. conventional CSF drainage with EVD open to 15 mmHg | Rapid weaning vs. gradual weaning of EVD treatment in SAH survivors | | Continuous CSF drainage with intermittent intracranial pressure (ICP) monitoring (open-EVD group) vs. continuous ICP monitoring with intermittent CSF drainage (monitor-ICP group) | Gradual wean vs. early clamp trial in nontraumatic SAH requiring EVD |
| Patients | 20 (13 in the aggressive group) | 965 (455 in the rapid wean group and 510 in the gradual weaning group) | | 60 patients (division between groups unknown) | 200 |
| Outcomes | | Development and timing of shunt dependency | | Incidence of cerebral artery vasospasm | VP shunt rate<br>NICU and hospital LOS<br>EVD duration<br>EVD related infections |
| Reason(s) for exclusion | Wrong intervention<br>Full-text not available | Wrong study design | Wrong study design | Wrong intervention | Wrong study design<br>Full-text not available |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 9 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8-9 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10-11 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 12 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 12-13 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 14 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 15 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | - |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | - |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | - |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 16 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 17 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 18 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

# Prompt closure vs. gradual weaning of external ventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid haemorrhage: A systematic review



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-040722.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 17-Oct-2020 |
| Complete List of Authors: | Capion, Tenna B.; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Lilja-Cyron, Alexander; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Juhler, Marianne; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Mathiesen, Tiit; Copenhagen University Hospital, Rigshospitalet, Department of Neurosurgery<br>Wetterslev , Jørn; Copenhagen University Hospital, Rigshospitalet, Copenhagen Trial Unit; Copenhagen University Hospital, Rigshospitalet, Copenhagen Trial Unit |
| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Intensive care |
| Keywords: | NEUROSURGERY, INTENSIVE & CRITICAL CARE, NEUROLOGY |
| | |

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# Prompt closure vs. gradual weaning of external ventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid haemorrhage: A systematic review

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**Keywords/MeSH terms:** Subarachnoid Hemorrhage/complications, Aneurysm, Hydrocephalus, Treatment outcome

**Word count:** 4593

## 1. ABSTRACT

**Objectives:** To summarize the evidence on benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aneurysmal subarachnoid haemorrhage (aSAH) based on randomized clinical trials in humans.

**Setting:** Randomized, clinical trials (RCT) comparing prompt closure vs. gradual weaning of external ventricular drainage in adult patients with hydrocephalus following aSAH were included.

**Participants:** Patients aged equal to or greater than 18 years with an external ventricular drain (EVD) due to hydrocephalus following aSAH were eligible for inclusion.

**Primary and secondary outcome measures:** Primary outcomes were all-cause mortality, any serious adverse event, rate of ventriculo-peritoneal (VP) shunt placement and quality of life. Secondary outcomes were patients with shunt failure, hospital and Neuro Intensive Care Unit (NICU) length of stay (LOS) and complications related to treatment with an EVD. Data permitted report of rate of VP shunt placement, and hospital and NICU LOS.

**Results:** Six studies were assessed in full-text. One RCT with 81 patients was included. Rate of VP shunt placement was 63.4 % in the rapid weaning group (i.e. prompt closure of the EVD; 41 patients) and 62.5% in the gradual weaning group (40 patients; $p = 0.932$). LOS in hospital and NICU was significantly shorter in the rapidly weaned group compared to the gradually weaned group (mean 19.1 vs. 21.5 days in hospital [$p = 0.03$]; and mean 14.1 vs. 16.9 days in NICU [$p = 0.0002$]). Data was insufficient to conduct meta-analysis, trial sequential analysis or subgroup analysis of heterogeneity and sensitivity. One RCT is currently ongoing.

**Conclusions:** We found insufficient evidence to favor any of the two strategies for EVD discontinuation in patients with hydrocephalus following aSAH.

**Trial registration:** This systematic review was preceded by a published protocol and is registered in the PROSPERO register under the ID number CRD42018108801

## 2. ARTICLESUMMARY

Strengths and limitations of this study

Strengths

1) Patient centered outcomes
2) Rigorous assessment of bias and the risk of random errors
3) GRADE assessment of the quality of the total evidence

Limitations

1) One included RCT
2) Recommendations from systematic reviews may suffer from the quality of the included trials

## 3. BACKGROUND

Aneurysmal SAH (aSAH) is a common and often devastating cerebrovascular disease accounting for approximately 7 % of all strokes.(1) Acute hydrocephalus due to blockage of cerebrospinal fluid (CSF) circulation occurs as a common and severe complication, which is treated with an external ventricular drain (EVD) in the acute phase. An EVD enables removal of CSF and subsequently management of intracranial pressure (ICP).(2,3) Up to 37 % of patients with an EVD develop chronic hydrocephalus during the course of the disease, requiring permanent diversion of CSF via a ventriculo-peritoneal (VP) shunt.(2) How to increase safety of EVD discontinuation and reduce the need for a VP-shunt is debated. Two different strategies are typically being used to assess for dependence of drainage; prompt closure or gradual weaning of the EVD. The latter is performed by stepwise increase of drainage resistance to outflow over days. It is unknown whether these two strategies result in differentiated clinical outcomes, different risks for VP shunt placement or whether they lead to different complication rates of EVD and VP-shunt treatment.

### 3.1 Description of the condition

In adults, CSF production is constant at approximately 500 ml/day. Thus CSF circulation and absorption occur at a similar rate keeping the system in balance. Post-haemorrhagic hypersecretion of CSF or obstruction of CSF circulation and absorption result in hydrocephalus.(4) The reported prevalence of hydrocephalus following aSAH ranges between 6 % and 67 %, and three stages of hydrocephalus are generally recognized: acute (0-3 days after SAH), subacute (4-13 days after SAH) and chronic ($\geq$ 14 days after SAH).(3)

### 3.2 Description of the intervention

Scientific data to define timing and choice of strategy for discontinuation and removal of an EVD inserted to treat hydrocephalus following aSAH is sparse. In some patients circulation of CSF returns to normal within days or weeks, permitting the EVD to be removed with ICP within normal range and no further need for treatment. In other patients, chronic hydrocephalus evolves with the need for an implanted permanent drainage solution (a VP shunt)(5) which diverts CSF from the brain ventricles to the abdomen where it is absorbed. Prolonged duration of EVD treatment as seen in gradual weaning of the EVD is an attempt to await potential return of normal CSF circulation and thereby avoid a permanent shunt. However, the risk of serious and potentially fatal infection (ventriculitis, meningitis, cerebral abscess) increases with prolonged EVD treatment. Conversely, early discontinuation may involve risks associated with increased ICP and acute hydrocephalus and possibly increased risk for placement of a permanent shunt.

### 3.3 How the intervention might work

The process of identifying patients who will need a permanent VP shunt involves a trial of closure of the EVD. The main argument in favour of prompt closure of the EVD is to minimize the treatment period and thereby the risk of infection. Subsequently, patients could potentially be discharged earlier from the hospital and thus begin rehabilitation sooner. The arguments in favour of weaning by gradually increasing drainage resistance involves time for reestablishment of normal CSF circulation, and thus less drastic changes in ICP with potential protection of brain tissue.

### 3.4 Why it is important to do this review

A possible difference between the two treatment strategies is important to identify as difference in treatment may affect patient outcomes. Insertion of a VP shunt is best defined as a surrogate outcome measure in the present context, as the indication for the procedure seems to vary throughout and the procedure is associated with risks for the patient (i.e. mechanical shunt dysfunction and shunt related infections) and increased medical costs for society as shunt complications frequently require additional hospitalizations and surgical interventions.

Previous reviews within this field have compared the two EVD discontinuation strategies in patients with hydrocephalus following aSAH via comprehensive literature searches without pre-published protocols or pre-defined hypotheses or data extraction plans, and without a validated rating of the available evidence.(6,7) A review that methodologically meets the rigorous demands for systematic reviews as

defined by the PRISMA guidelines (and 2015 PRISMA-P statement) provides the highest possible impact for researchers to use in forthcoming work and investigation of this medical issue.(8)

## 4. OBJECTIVES

To summarize the evidence on benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH based on randomized clinical trials in humans.

## 5. METHODS

### 5.1 Criteria for considering studies for this review

#### 5.1.1 Types of studies

This systematic review was conducted in accordance with PROSPERO registration (CRD42018108801) and a pre-published protocol.(9) The recommendations from the Cochrane Collaboration, the PRISMA guidelines for systematic reviews (8) and the GRADE assessment were followed.(10)

Randomized clinical trials (RCT) comparing prompt closure vs. gradual weaning of external ventricular drainage in patients with aSAH were included in qualitative evaluations of intervention effects in this systematic review. Additionally, observational studies were included in an appendix enumerating findings of serious adverse events (SAE).

Studies were assessed without consideration of publication status, blinding status or language. No unpublished trials or trials using quasi-randomization were included.

#### 5.1.2 Types of participants

Patients aged equal to or greater than 18 years with an EVD due to hydrocephalus following aSAH were eligible for inclusion.

#### 5.1.3 Types of interventions

Interventions studied involve prompt closure, i.e. the direct closure of the EVD, vs. gradual weaning, i.e. a gradual increase of resistance to outflow over days, of external ventricular drainage due to hydrocephalus following aSAH.

#### 5.1.4 Types of outcome measures

Predefined primary outcomes include death from any cause, any SAE defined according to the International Conference of Harmonization of Good Clinical Practice (ICH-GCP)(11), complications and adverse events

specific for EVD and VP shunt systems (clinical and radiological signs of shunt obstruction, and clinical and microbiological signs of ventriculitis and shunt infection), rate of permanent VP shunt placement and quality of life measured (QoL) with any score.

Predefined secondary outcomes comprise number of shunt interventions following the primary shunt insertion (surgical shunt interventions for any reason) within the longest follow-up in each trial, total hospital and NICU length of stay (LOS), and EVD related complications (ventriculitis defined as positive CSF culture, clinically relevant intracranial haemorrhage requiring surgical evacuation or additional surgical procedure secondary to EVD misplacement).

## 5.2 Search methods for identification of studies

### 5.2.1 Electronic searches

Searches were performed without language or date restrictions. The following electronic databases were searched: The Cochrane Library's Central Register of Controlled trials (CENTRAL), MEDLINE (1946 to date) (Ovid SP), EMBASE (1974 to date) (Ovid SP), LILACS (1982 to date) (BIREME), Science Citation Index Expanded (1900 to November 2018) and Conference Proceedings Citation Index – Science (1990 to November 2018) (Web of Science). The preliminary search was performed on November 28th 2018 and repeated on January 20th 2020. The search strategies can be seen in Appendix 1.

### 5.2.2 Searching other resources

Studies included in the full text screening were hand searched for supplemental studies not registered in the electronic searches. Main authors of studies were contacted for any missed, unreported or ongoing trials and to retrieve relevant data.

## 5.3 Data collection and analysis

Main authors of studies included in the trial were contacted in case their publication did not contain sufficient information for risk of bias assessment and data extraction of our chosen outcomes.

### 5.3.1 Selection of studies

Two review authors (TC and ALC) independently evaluated all relevant references and provided a detailed description of included and excluded trials.

### 5.3.2 Data extraction and management

Titles and abstracts were screened in order to identify studies that were eligible. TC and ALC independently extracted and collected data using the Covidence software (*Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia*). We were not blinded to the author, institution or the publication source of trials. Disagreements were resolved by JW.

Review Manager Software (*Review Manager (RevMan) [Computer program], version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014*) was used as statistical software.

### 5.3.3 Assessment of risk of bias in included studies

TC and ALC independently conducted the assessment of risk of bias using The Cochrane Collaboration's recommended tool for assessing risk of bias. Disagreements were resolved by JW.

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. 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 of the quality of evidence for the results of each outcome.(12)

### 5.3.4 Dealing with missing data

Main authors of included trials were contacted in order to retrieve missing data.

For further details about the handling of missing data, and for details regarding assessment of heterogeneity, reporting bias, data synthesis, meta-analysis, trial sequential analysis, and subgroup and sensitivity analysis, please see published review protocol.(9)

### 5.3.5 GRADE

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate and assess the quality of the evidence for each outcome.(10) A summary of findings table was produced summarizing the quality of evidence for each outcome.

## 6. R E S U L T S

### 6.1 Description of studies

### 6.1.1 Results of the search

We identified 751 references via a primary search in November 2018 and an updated search in January 2020. Fifty-six references were removed as duplicates, leaving 695 to be screened for title and abstract. Of these, 6 studies were assessed in full-text. We found one RCT which met the inclusion criteria(13) (figure 1) and one observational study to be included in appendix(14) (appendix 2). No studies describing prompt closure vs. gradual weaning of external ventricular drainage in other conditions such as spontaneous intracranial hemorrhage were found.

### 6.1.2 Included studies

The included RCT by Klopfenstein et al. from 2004(13) randomized 81 adult patients with hydrocephalus following aSAH to either rapid or gradual weaning of the EVD. A rapid wean signified prompt closure of the EVD at time of intervention, whereas gradual weaning comprised four steps of increasing drainage resistance to outflow ending at complete closure of the EVD. Of the 81 randomized patients, 41 were in the rapidly weaned group and 40 patients were in the gradually weaned group. The primary outcome of this trial was rate of VP shunt placement. Secondary outcomes were i) number of days in which the EVD was in place; ii) number of days the patient spent in the ICU; and iii) overall duration of hospital stay.
All patients who failed either form of EVD discontinuation underwent shunt placement, resulting in equal shunt rates for the two groups. In the gradually weaned group the EVD remained in place for significantly longer time, while LOS in hospital and NICU were significantly longer for the gradually weaned group. No data were available for death by any cause, SAE or QoL at longest follow-up.
The authors concluded that gradual weaning provides no advantage over prompt closure in terms of rate of VP shunt placement, and that prompt closure should as such be pursued in the treatment of patients with aSAH due to shorter LOS in hospital and NICU and shorter time with EVD in place.
Contact by email to the corresponding and last author of this study in order to retrieve additional relevant data was attempted without result.

One observational cohort study comparing prompt closure vs. gradual weaning of EVD treatment in patients with aSAH was included in an appendix enumerating adverse effects (Appendix 2).(14) The study by Jabbarli et al. from 2018 compared treatment effects in two individual German institutions using different discontinuation strategies for external ventricular drainage in patients with aSAH. Outcomes were development and timing of shunt dependency. The authors concluded that patients treated by rapid weaning (i.e. prompt closure) of the EVD had significantly higher risk of getting a VP shunt and that gradual weaning led to longer EVD treatment but not in the expense of higher risk of drain related infections.

Contact by email to the corresponding author of this study in order to retrieve additional relevant data was attempted without result.

### 6.1.3 Excluded studies

Of the six studies included in the full-text screening, five studies were excluded.

One study was excluded due to wrong study intervention. The randomized, clinical trial by Olson et al. from 2013 compared continuous vs. intermittent external ventricular drainage in patients with an EVD due to hydrocephalus following aSAH. The study was terminated after the inclusion of 60 patients due to a higher complication rate in the continuous drainage group.(15)

Two of the excluded studies were conference papers to which full-texts were not available. In one of these studies, authors carried out a prospective, randomized pilot study to determine the feasibility of randomizing patients with an EVD after aSAH to either aggressive or conventional external ventricular drainage. The authors included 20 patients of which 13 were in the aggressive arm, and concluded that randomization is possible. The corresponding author to this study has via email informed that completion of the article was not pursued, nor was further progression with an RCT.

The second study was an abstract of a retrospective assessment of 200 patients with an EVD due to non-traumatic (aneurysmal) SAH(16) comparing gradual wean and early clamp trial of the EVD. The authors compared rate of VP shunt placement, NICU and hospital LOS, EVD duration and rate of EVD related infections and concluded that an early clamp trial was associated with fewer complications and shorter LOS compared to gradual weaning.

The last two references were excluded due to wrong study design; one was an observational study(14) carried out in 2018 which evaluated the role of EVD weaning on rate of VP shunt placement in 965 patients with aSAH. The authors concluded that at the expense of longer treatment, gradual EVD weaning may decrease the risk of shunt dependency without an additional risk of CSF infection. The second reference omitted due to wrong study design was a comment to the study by Jabbarli et al.(14), featured in the end of the article as contribution.

Details of the 5 excluded studies can be seen in appendix 3.

### 6.2 Risk of bias in included studies

Using the Cochrane Collaboration's tool for assessing risk of bias we found that the included study had limitations in design and execution severe enough to downgrade the quality of evidence. No information regarding allocation table or concealment was provided which resulted in unclear risk of selection bias.

Participants and personnel were not blinded to the intervention due to the nature of the intervention. Patients were randomized at time of enrollment. The timing of intervention was decided by a treating physician not involved in the trial execution but blinded to the outcome of the randomization. No details describing how the randomization process was performed were provided. We assessed the risk of performance bias and detection bias as high.

Outcome was reported for the 51 patients out of 81 who received a VP shunt. Follow-up status for the remaining 30 patients was not reported. Intent-to-treat analysis was described for the primary outcome but not for secondary outcomes. The numbers of eligible, included and excluded patients were provided. Reasons for patient exclusion and withdrawal were not specified neither were information about the handling of the excluded patients in terms of randomization or intention-to-treat analysis. The risk of attrition bias was due to these limitations assessed as unclear. Further, patient-centered outcomes such as mortality, number of SAE, complications related to EVD and VP shunt treatment and QoL were not reported which made risk of reporting bias high. No study protocol was published before the study paper and no sample size calculations were provided which might have led to data driven reporting bias.

These limitations are severe in their generation of the overall risk of bias as they might individually and combined cause bias to the execution of the study and to the randomization process which may cause systematic bias in the inclusion and division of patients and thus to the results of the study. Based on the assessed domains the overall risk of bias of the included study was assessed as high (figure 2).

### 6.3 Effects of interventions

The only primary outcome for which the included RCT provided data was rate of VP shunt placement. All patients who failed either form of EVD discontinuation underwent shunt placement, resulting in a shunt rate of 63.4 % and 62.5 % for rapid or gradual wean, respectively ($p = 0.932$). Certainty for this outcome assessed via the GRADE approach was considered very low primarily due to very serious risk of bias, very serious imprecision and serious indirectness.

Secondary outcomes for which data were available were time with EVD in place, and hospital and NICU LOS. In the rapidly weaned group the EVD remained in place for significantly shorter time compared to the gradually weaned group (mean of 12.7 vs. 15.8 days, $p = 0.000009$). LOS in hospital and NICU was also shorter for the rapidly weaned group (19.1 vs. 21.5 days in hospital [$p = 0.03$]; 14.1 vs. 16.9 days in NICU [$p = 0.0002$]). The certainty for these outcomes was equally considered very low based on very serious risk of bias, very serious imprecision and serious indirectness.

The power of the included RCT (81 patients) does not reach required information size (RIS) to conduct a reliable and conclusive meta-analysis which in size is expected to be at least that of the sample size of one

well-powered RCT for a reliable detection or rejection of an anticipated intervention effect.(17) A study with few patients and few events, and thus wide confidence intervals, raises imprecision and uncertainty about the results, as is also the result in the present included RCT.

### 6.4 Patient and public involvement

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

## 7. DISCUSSION

This systematic review aimed at assessing the evidence of benefits and harms of prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH. We conducted an extensive literature search which resulted in just 6 studies evaluated in full text. We included one RCT with 81 patients which concluded that prompt closure is safe and reduce LOS in hospital and NICU. We assessed however the RCT by Klopfenstein et al. to be of overall low quality with high risk of bias and thus insufficient in order to provide high-quality evidence to support or refute either of the two investigated strategies for EVD discontinuation. Despite the assessed quality of the RCT, the current international guidelines covering this issue base their recommendations solely on the results from this study.(18) Previous reviews differ in design and methodology, they do not assess the quality of included studies in detail, and they support the recommendations for prompt closure as discontinuation strategy despite the above mentioned shortages in evidence.(6,7) There is currently no high-quality evidence to cover this information gap.

The present systematic review is the first of its kind to address the question of EVD discontinuation strategy after aSAH by assessment of included studies using the Cochrane risk of bias tool and the GRADE approach, and it disagrees with previous review conclusions on the applicability of the results of the included RCT in international recommendations and guidelines.

### 7.1 Summary of main results

One RCT with 81 patients was included in this systematic review. The included trial showed very serious risk of bias and imprecision and an overall very low quality assessment based on the GRADE approach and the Cochrane risk of bias tool. Required information size to provide reliable meta-analysis and TSA on our chosen outcomes was not reached and it was impossible to conduct subgroup and sensitivity analyses to investigate reasons for heterogeneity.

### 7.2 Overall completeness and applicability of evidence

There is insufficient evidence to favor any of the two investigated strategies for discontinuation of external ventricular drainage in patients with hydrocephalus following aSAH.

### 7.3 Quality of the evidence

Based on GRADE the certainty of the evidence for the primary outcome and the two secondary outcomes, for which data was provided, was in all cases assessed as 'very low'. These assessments were mainly based on very serious risk of bias, very serious imprecision and serious indirectness (figure 3).

For the remaining 3 primary outcomes and 2 secondary outcomes which this systematic review sought to evaluate there were no available data.

### 7.4 Potential biases in the review process

The authors to this review has based on the preliminary literature search in November 2018 initiated and launched an RCT comparing prompt closure vs. gradual weaning of external ventricular drainage in patients with hydrocephalus following aSAH which is currently ongoing. We might as such be biased in assessing methods within this field as we have previously done extensive literature search within this area of research.

### 7.5 Agreement and disagreement with other reviews

Chung et al. conclude in a 2019 literature review (covering literature until 2017) that a recommendation towards an early EVD clamp (i.e. prompt closure) is possible based on the evidence of the RCT by Klopfenstein et al.(7) In this literature search, the only included trial (Klopfenstein) is assessed via pragmatic evaluation and not via validated tools as the Cochrane tool for assessing risk of bias or the GRADE approach.

In an evidence-based consensus statement from the Neurocritical Care Society in 2015 (covering literature until 2014) the authors conclude that the RCT by Klopfenstein et al. demonstrated that rapid weaning can be accomplished safely.(6) The society simultaneously underlines that the recommendation is based upon one RCT with limited number of included patients. The recommendation comprises early EVD discontinuation in order to favor a decreased risk of EVD related infections.

Our review disagrees with the conclusions of these previous reviews in the essence that we do not believe that a recommendation towards a specific weaning strategy is possible based on current available scientific data.

## 8. AUTHORS' CONCLUSIONS

### 8.1 Implications of practice

There is insufficient evidence to favor any of the two investigated strategies for EVD discontinuation in adult patients with external ventricular drainage due to hydrocephalus following aSAH. Current guidelines support prompt closure of the EVD as discontinuation strategy based on the RCT described in this systematic review which has shown to be of very low quality and thus possess deficiencies severe enough to downgrade its level of evidence. Subgroup analyses were not possible to complete due to limited data and this systematic review do not allow for recommendations for clinical practice.

### 8.2 Implications for research

Larger, high-quality, randomized, clinical trials with transparent objective criteria for randomization, pre-published protocols to avoid data-driven reporting bias, independent sequence allocation with proper concealment and description of blinding incl. of outcome assessors are needed to provide reliable prospective data before conclusions regarding benefits and harms of this widely used treatment practice can be drawn safely.

### Acknowledgements

The group of authors would like to thank search coordinator Sarah Klingenberg from Copenhagen Trial Unit for providing the search strategy for this systematic review.

### Contributions of authors

1. Conception or design of the work: TC, ALC, MJ, TM, JW
2. Data collection: TC, ALC, JW
3. Data analysis and interpretation: TC, JW
4. Drafting the article: TC, ALC, JW
5. Critical revision of the article: TC, ALC, MJ, TM, JW
6. Final approval of the version to be published: TC, ALC, MJ, TM, JW

### Declaration of interest

Dr Wetterslev has been a member of the taskforce at Copenhagen Trial Unit to develop theory, manual, and software for doing Trial Sequential Analysis presently freeware at www.ctu.dk/tsa.

## Funding

Dr Capion has received funding from the Research Council at Copenhagen University Hospital Rigshospitalet (Grant no. E-23565-03). The funding party is not involved in the conduct of this review.

## Data sharing statement

Extracted data is available upon reasonable request and only after approval from co-authors and relevant regulatory approvals.

### Figure legends

Figure 1: *Figure 1: PRISMA flow diagram showing the results of the search*

Figure 2: *Figure 2: Risk of bias assessment. Red = high risk; yellow = unclear risk.*

Figure 3: *Figure 3: Summary of findings table showing the rating of the quality of the evidence for each outcome using the GRADE assessment.*

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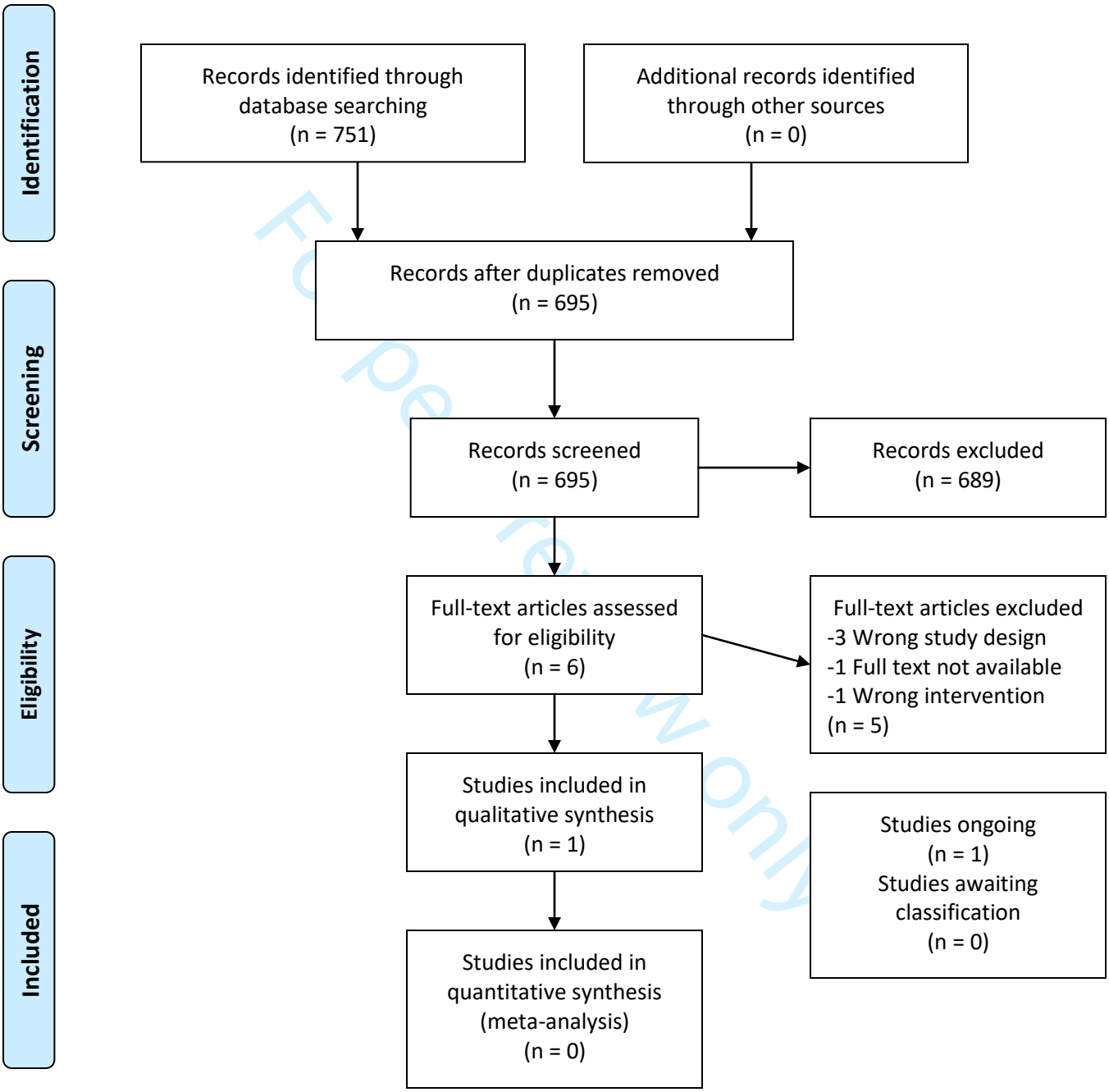
## PRISMA Flow Diagram






*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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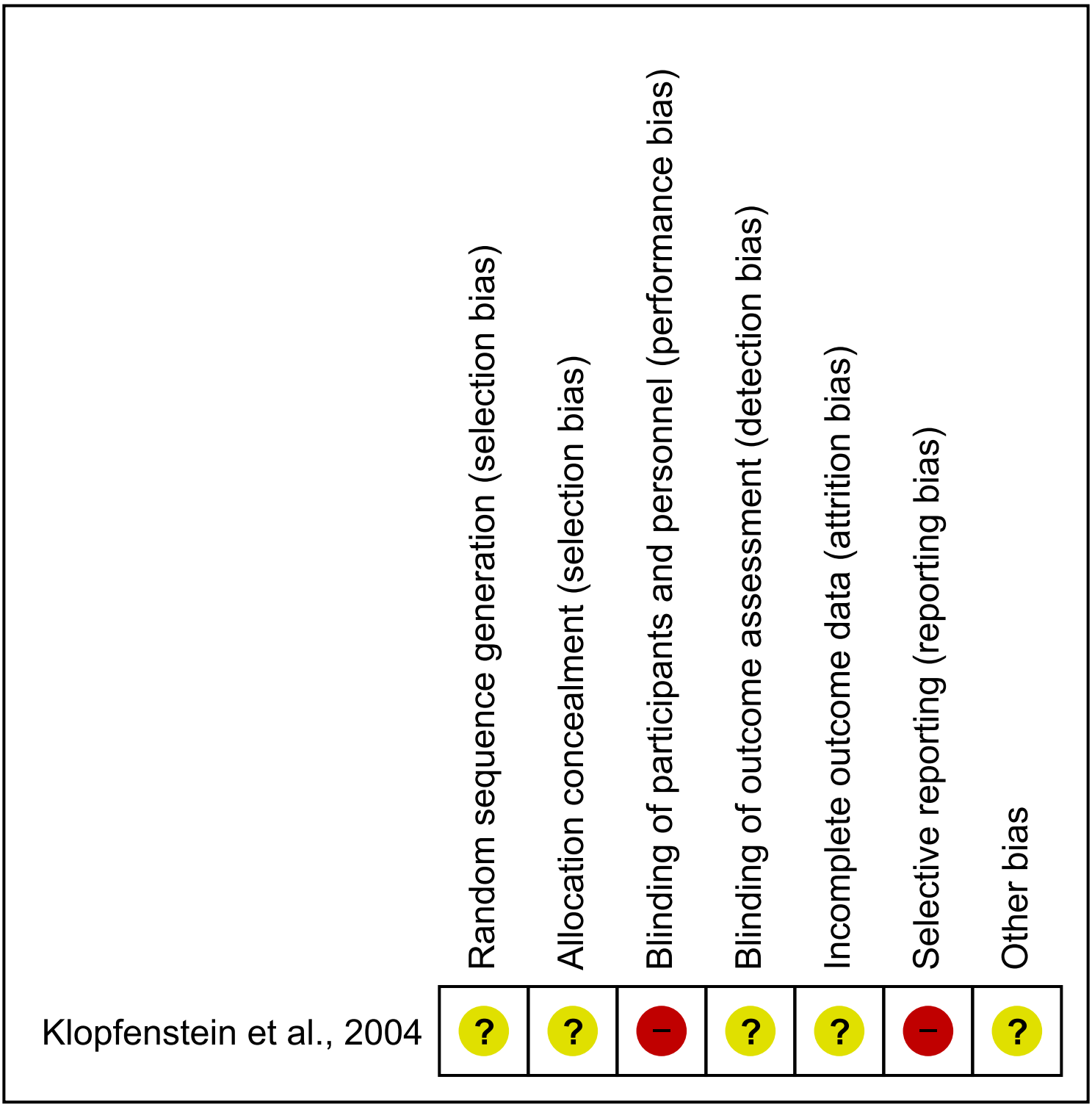
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Klopfenstein et al., 2004
?
?
–
?
?
–
?

**Summary of findings:**

## Prompt closure compared to gradual weaning in discontinuation of external ventricular drainage

**Patient or population**: adult patients with hydrocephalus following aneurysmal subarachnoid haemorrhage
**Setting**: discontinuation of external ventricular drainage
**Intervention**: prompt closure
**Comparison**: gradual weaning

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with gradual weaning | Risk with prompt closure | | | | |
| Death - not reported | - | - | - | - | - | |
| Serious Adverse Events - not reported | - | - | - | - | - | |
| Rate of permanent VP-shunt implementation<br>follow up: mean 7.5 months | 63 per 100 | **63 per 100**<br>(46 to 89) | **RR 1.01**<br>(0.73 to 1.42) | 81<br>(1 RCT) | ⊕◯◯◯<br>VERY LOW<br>a,b,c,d,e,f | The evidence is very uncertain about the effect of prompt closure on rate of permanent VP-shunt implementation. |
| Quality of life - not reported | - | - | - | - | - | |
| Total hospital length of stay (LOS) | The mean total hospital length of stay was **21.5** days | mean **2.4 days lower**<br>(17.1 lower to 12.3 higher) | - | 81<br>(1 RCT) | ⊕◯◯◯<br>VERY LOW<br>a,b,c,d,e,f | Prompt closure may reduce/have little to no effect on total hospital length of stay but the evidence is very uncertain. |
| Total Neuro Intensive Care Unit length of stay (NICU LOS) | The mean total Neuro Intensive Care Unit length of stay was **16.9** days | mean **2.8 days lower**<br>(11.4 lower to 5.8 higher) | - | 81<br>(1 RCT) | ⊕◯◯◯<br>VERY LOW<br>a,b,c,d,e,f | Prompt closure may reduce/have little to no effect on total Neuro Intensive Care Unit length of stay but the evidence is very uncertain. |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**
**a**. Lack of information regarding sequence allocation and concealment of allocation table; **b**. Lack of blinding; **c**. Missing description of randomization; **d**. Mortality and Serious Adverse Events not reported as patient important outcomes
**e**. Very few events; f. Wide confidence intervals.

**Search strategies for**
**'Prompt closure vs. gradual weaning of extraventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid hemorrhage'**
**(T Capion)**
**Preliminary searches performed 17 January 2020**

| | |
|---|---|
| **Total number identified** | **1099 records** |
| **Number of duplicates removed** | **367 records** |
| **Number in list** | **732 records** |
| **Number of new records sent to authors** | **84 records** |

**Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2020, Issue 1) (12 hits)**

#1 MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2 (subarachnoid* or SAH)
#3 #1 or #2
#4 MeSH descriptor: [Drainage] explode all trees
#5 MeSH descriptor: [Ventriculostomy] explode all trees
#6 (drain* or ventricul* or evd)
#7 #4 or #5 or #6
#8 MeSH descriptor: [Device Removal] explode all trees
#9 (cessation* or clos* or weaning)
#10 #8 or #9
#11 #3 and #7 and #10

**MEDLINE Ovid (1946 to January 2020) (313 hits)**

1. exp Subarachnoid Hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. exp Drainage/
5. exp Ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 4 or 5 or 6
8. exp Device Removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 8 or 9
11. 3 and 7 and 10

**Embase Ovid (1974 to January 2020) (353 hits)**

1. exp subarachnoid hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. 1 or 2
4. exp drain/
5. exp ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. 4 or 5 or 6
8. exp device removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. 8 or 9
11. 3 and 7 and 10

**LILACS (Bireme; 1982 to January 2020) (4 hits)**
(subarachnoid$ or SAH) [Words] and (drain$ or ventricul$ or evd) [Words] and (cessation$ or clos$ or weaning) [Words]

**Science Citation Index Expanded (1900 to January 2020) and Conference Proceedings Citation Index – Science (1990 to January 2020) (Web of Science) (235 hits)**
#4 #3 AND #2 AND #1
#3 TS=(cessation* or clos* or weaning)
#2 TS=(drain* or ventricul* or evd)
#1 TS=(subarachnoid* or SAH)

**Search strategies for**
**'Prompt closure vs. gradual weaning of extraventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid hemorrhage'**
**(T Capion)**
**Preliminary searches performed 28 November 2018**

| | |
|---|---|
| **Total number identified** | **1033 references** |
| **Number of duplicates removed** | **366 references** |
| **Number in list** | **667 references** |

**Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2018, Issue 11) (6 hits)**

#1 MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2 (subarachnoid* or SAH)
#3 #1 or #2
#4 MeSH descriptor: [Drainage] explode all trees
#5 MeSH descriptor: [Ventriculostomy] explode all trees
#6 (drain* or ventricul* or evd)
#7 #4 or #5 or #6
#8 MeSH descriptor: [Device Removal] explode all trees
#9 (cessation* or clos* or weaning)
#10 #8 or #9
#11 #3 and #7 and #10

**MEDLINE Ovid (1946 to November 2018) (299 hits)**

1. exp Subarachnoid Hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. exp Drainage/
5. exp Ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 4 or 5 or 6
8. exp Device Removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 8 or 9
11. 3 and 7 and 10

**Embase Ovid (1974 to November 2018) (496 hits)**

1. exp subarachnoid hemorrhage/
2. (subarachnoid* or SAH).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. 1 or 2
4. exp drain/
5. exp ventriculostomy/
6. (drain* or ventricul* or evd).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. 4 or 5 or 6
8. exp device removal/
9. (cessation* or clos* or weaning).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. 8 or 9
11. 3 and 7 and 10

**LILACS (Bireme; 1982 to November 2018) (3 hits)**
(subarachnoid$ or SAH) [Words] and (drain$ or ventricul$ or evd) [Words] and (cessation$ or clos$ or weaning) [Words]

**Science Citation Index Expanded (1900 to November 2018) and Conference Proceedings Citation Index – Science (1990 to November 2018) (Web of Science) (229 hits)**
#4 #3 AND #2 AND #1
#3 TS=(cessation* or clos* or weaning)
#2 TS=(drain* or ventricul* or evd)
#1 TS=(subarachnoid* or SAH)

# Appendix 2: Observational studies

| Study | Objective | Method | Outcomes | Serious Adverse Events |
|---|---|---|---|---|
| Jabbarli R. et al.: *Gradual External Ventricular Drainage Weaning Reduces The Risk of Shunt Dependency After Aneurysmal Subarachnoid Hemorrhage: A Pooled Analysis* | To evaluate the role of external ventricular drainage (EVD) weaning on risk of shunt dependency after SAH | Observational cohort study | Development and timing of shunt dependency in SAH survivals | Shunt dependency: RW: 34.73%, GW: 27.45% (OR 0,71, CI: 0.54-0.94, P = 0,018) |

## Appendix 3: Excluded studies

| | Study # 1 | Study # 2 | Study # 3 | Study # 4 | Study # 5 |
|---|---|---|---|---|---|
| Title | *Csf diversion in aneurysmalsubarachnoid hemorrhage: How low should we go?* | *Gradual External Ventricular Drainage Weaning Reduces The Risk of Shunt Dependency After Aneurysmal Subarachnoid Hemorrhage: a Pooled Analysis* | A comment to: *"Gradual External Ventricular Drainage Weaning Reduces The Risk of Shunt Dependency After Aneurysmal Subarachnoid Hemorrhage: a Pooled Analysis"* | *Continuous cerebral spinal fluid drainage associated with complications in patients admitted with subarachnoid hemorrhage* | *An early EVD clamp trial approach for subarachnoid hemorrhage is associated with a lower ventriculoperitoneal shunt rate, shorter length of stay, and fewer EVD complications-a retrospective study* |
| Authors | Fugate J; Rabenstein A; Wijdicks E; Freeman W; Lanzino G. | Jabbarli R; Pierscianek D; ROlz R; Reinhard M; Darkwah Oppong M; Scheiwe C; Dammann P; Kaier K; Wrede KH; Shah M; Zentner J; Sure U. | Lilja-Cyron A; Mathiesen T. | Olson DM; Zomorodi M; Britz GW; Zomorodi AR; Amato A; Graffagnino C. | Rao S; Wolcott ZC; Chung DY; Sheriff F; Khawaja A; Patel AB; Kimberly WT; Rordorf GA. |
| Year of publication | 2014 | 2018 | 2018 | 2013 | 2017 |
| Journal | Neurology CONFERENCE START: 2014 Apr 26 CONFERENCE END: 2014 May 3 2014;82(10 SUPPL. 1): Lippincott Williams and Wilkins MISC1 - 20140527 2014 | Operative Neurosurgery (hagerstown, md 2018;15(5):498-504 United States NLM (Medline) | Operative neurosurgery 2018;(5):504-504 2018 | Journal of neurosurgery ;119(4):974-980 United States American Association of Neurological Surgeons (1224 West Main Street Suite 450, Charlottesville VA 22903, United States) | Neurocritical care 2017; Conference: 15th Annual Meeting of the Neurocritical Care Society, NCS 2017. United States. 27(2 Supplement 1):S3 Netherlands Humana Press Inc. 2017 |
| Objective | To evaluate the feasibility of | To evaluate the role of external ventricular | Comment to existing article | To explore whether continuous or | To determine the optimal approach of |

| | | | | | |
|---|---|---|---|---|---|
| | randomizing patients with aneurysmal subarachnoid haemorrhage and hydrocephalus to "aggressive" vs "conventional" cerebrospinal drainage | drainage (EVD) weaning on risk of shunt dependency after SAH | | intermittent CSF drainage was superior for reducing vasospasm | gradual wean vs. early clamp trial in nontraumatic SAH requiring EVD |
| Study design | 2-center, prospective, randomized pilot study | Observational cohort study | | Randomized clinical trial | Retrospective study |
| Intervention | Aggressive CSF drainage with EVD open to 5 mmHg vs. conventional CSF drainage with EVD open to 15 mmHg | Rapid weaning vs. gradual weaning of EVD treatment in SAH survivors | | Continuous CSF drainage with intermittent intracranial pressure (ICP) monitoring (open-EVD group) vs. continuous ICP monitoring with intermittent CSF drainage (monitor-ICP group) | Gradual wean vs. early clamp trial in nontraumatic SAH requiring EVD |
| Patients | 20 (13 in the aggressive group) | 965 (455 in the rapid wean group and 510 in the gradual weaning group) | | 60 patients (division between groups unknown) | 200 |
| Outcomes | | Development and timing of shunt dependency | | Incidence of cerebral artery vasospasm | VP shunt rate<br>NICU and hospital LOS<br>EVD duration<br>EVD related infections |
| Reason(s) for exclusion | Wrong intervention<br>Full-text not available | Wrong study design | Wrong study design | Wrong intervention | Wrong study design<br>Full-text not available |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 9 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8-9 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10-11 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 12 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 12-13 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 14 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 15 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | - |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | - |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | - |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 16 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 17 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 18 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.