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a study protocol**

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BMJ Open Descriptive registry study on outcome and complications of external ventricular drainage treatment of intraventricular haemorrhage in a Danish cohort: a study protocol

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ABSTRACT

Introduction Intraventricular haemorrhage (IVH) is associated with high morbidity and mortality. External ventricular drainage (EVD) has been shown to decrease mortality. Although EVD is widely used, outcome and complication rates in EVD-treated patients with IVH are not fully elucidated. This study aims to describe EVD complication rates and outcomes in patients with primary and secondary IVH at two university hospitals in Denmark. The study will provide a historical reference of relevant endpoints for use in future clinical trials involving patients with IVH.

Methods and analysis This descriptive, multicentre registry study included adult patients (age 18+) with primary or secondary IVH and treated with at least one EVD between 2017 and 2021 at Aarhus University Hospital or Odense University Hospital. Patients are identified using the Danish National Patient Register. Data are collected and recorded from patient medical records. Relevant descriptive statistics and correlation analyses will be applied.

Ethics and dissemination Ethical approval and authorisation to access, store and analyse data have been obtained (Central Denmark Region Committee on Health Research Ethics). The research lead will present the results of the study. Data will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology and results submitted for publication in peer-reviewed journals.

INTRODUCTION

Intracerebral haemorrhage (ICH) is associated with high mortality or severe, long-term neurological disability.^{1–3} The incidence of ICH is 24.6 per 100 000 person years,^{4 5} and approximately 10% suffer an intraventricular haemorrhage (IVH). IVH is associated with higher mortality and neurological morbidity than haemorrhages with no intraventricular extension.^{6–9} Patients with IVH have a high risk of hydrocephalus and increased intracranial pressure (ICP).^{10 11}

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study benefits from Denmark's socialised healthcare system, which ensures uniform treatment access, training and licensing, thereby reducing referral bias and increasing cohort homogeneity.
- ⇒ The study offers a comprehensive analysis of technical aspects and outcomes of external ventricular drainage (EVD) performance, facilitating direct endpoint comparison for future catheter-based intraventricular haemorrhage (IVH) technology trials.
- ⇒ The study examines Graeb-scored IVH across various etiologies, shedding light on how intraventricular blood affects EVD performance.
- ⇒ The study's exclusive emphasis on IVH restricts the applicability of its findings to other EVD indications like traumatic brain injury and subarachnoid haemorrhage without intraventricular breakthrough.
- ⇒ The study's retrospective and observational design limits its ability to assess causality between outcomes and predictive variables.

Current IVH treatment involves extensive neurointensive care and external ventricular drainage (EVD). EVD is associated with several complications, such as occlusion of the EVD due to blood or inflammatory debris. This leads to malfunction and increase in the ICP,¹² and potentially to a need for flushing or surgical replacement of the catheter with inherent risks of brain haemorrhage or secondary infection.^{13–15} Passive drainage limits the haematoma evacuation to the time of spontaneous degradation, which is typically 2–3 weeks. The length of EVD treatment may increase the risk of infection and length of stay in the intensive care unit (ICU), as well as increased financial burden and a significant demand of time and resources.^{13 16 17} The rate

of complications, patient outcomes and the financial costs of EVD treatment are not fully elucidated. It is important to fill this knowledge gap to clearly outline the clinical challenges and to provide a historical reference base for comparison of future trial endpoints testing new technologies (eg, the ACTIVE Study, clinicaltrials.gov identifier NCT05204849).¹⁸ To the best of our knowledge, no studies have investigated the complications and patient outcome associated with EVD treatment in a Northern European setting. The present study will serve as a historical reference for direct comparison with clinical trials on similar endpoints and provide a reference for future studies evaluating new technologies and solutions.

Objective

To describe the overall clinical outcome and complications of EVD treatment in patients with IVH.

Primary objective

- ▶ To describe the overall complications of EVD treatment in patients with IVH.

Secondary objectives

- ▶ To describe clinical outcome and mortality in EVD treated patients with IVH.
- ▶ To identify risk factors for EVD complications in patients with IVH.

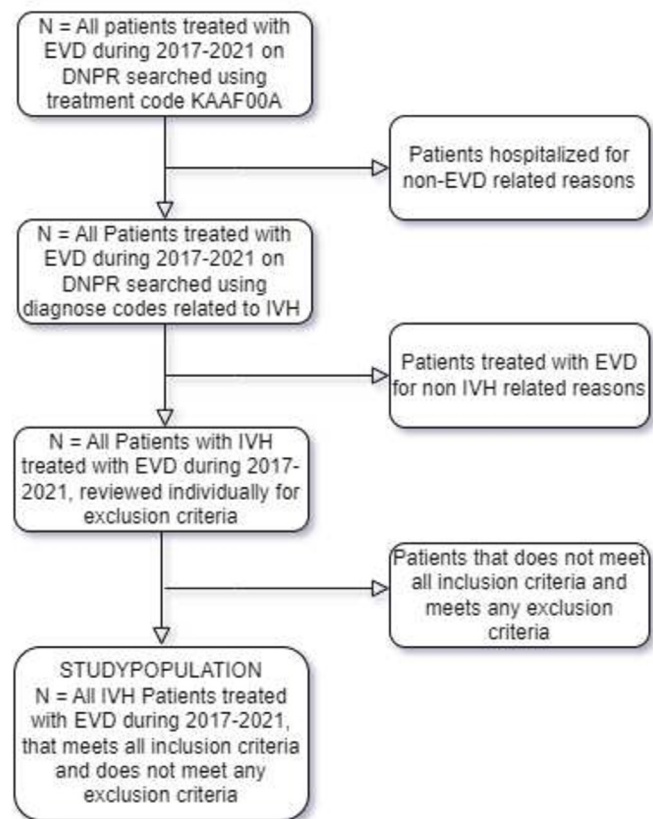


Figure 1 Flowchart of patient inclusion. DNPR, Danish National Patient Register; EVD, external ventricular drainage; IVH, intraventricular haemorrhage.

- ▶ To estimate financial costs and resource consumption burden of EVD treatment.
- ▶ To identify predictive factors associated with clinical outcome and mortality.
- ▶ To establish historical retrospective reference estimates of clinical endpoints and outcomes for clinical trials involving patients with IVH.

METHODS AND ANALYSIS

Study design

This is a descriptive, multicentre retrospective cohort study of adult patients (age 18+) with IVH undergoing EVD treatment at Aarhus University Hospital (AUH) and Odense University Hospital (OUH) in Denmark between 1 January 2017 and 31 December 2021. Data will be collected from patient medical records over an 8 month period starting on 1 February 2023.

Study population

Eligible patients will be identified in the Danish National Patient Register (DNPR) between 1 January 2017 and 31 December 2021, by combining procedural code for EVD insertion (KAAF00A), with the ICD-10 diagnosis codes for primary or secondary IVH (DI60, DI610, DI610A, DI611, DI611A, DI612, DI613, DI614, DI615, DI619, DI620 and DI629). A flowchart shows patient inclusion (figure 1). Eligibility will be decided based on data from patient medical records. We estimate a sample size of around 500 patients, based on the annual number of patients admitted to the participating hospitals.

Eligibility criteria

Inclusion criteria

1. Age 18 or older.
2. CT or MRI scan confirming IVH.
3. EVD treatment following IVH (< 72 hours from primary CT or MRI scan).

Exclusion criteria

4. Patients treated with other drainage technologies than passive EVD, for example, IRRAfflow.
5. Patients who underwent surgical evacuation of the IVH prior to EVD treatment, that is, endoscopic surgery or open surgery. Patients undergoing surgical removal of ICH components and surgical treatment of aneurysms, arteriovenous malformations, etc, will be accepted for inclusion.

Data collection

Data will be collected from patient medical records and managed and stored in REDCap (Research Electronic Data Capture), hosted by Aarhus University, Denmark. Data will include baseline demographics, outcome risk factors and outcome variables (defined below). The date of the IVH event will be considered as the patient inclusion date.

Variable definitions

Outcome variables

1. Presence of EVD complications. Complications are graded in accordance with the Common Terminology Criteria for Adverse Events:
 - a. EVD-related central nervous system (CNS) infections, defined as a positive cerebrospinal fluid (CSF) culture sample between time of EVD placement and hospital discharge. Samples are cultured and infectious agents are documented. Treatment is documented, including type of antibiotics, duration and route of administration.
 - b. EVD-related partial and complete occlusions. A partial occlusion is defined as slow moving or sluggish drainage, and complete occlusion is defined as ceased drainage, assessed by nurses and doctors. Furthermore, possible cause of occlusion is also included.
 - c. Surgical complications include haematoma formation in relation to EVD placement or removal, displacements during EVD treatment or misplacements of catheter.
2. Shunt dependency, defined as implantation of any ventriculoperitoneal shunt within 6 months following EVD treatment.
3. EVD replacement rate, defined as EVDs replaced using the same bolt and catheter canal.
4. Functional outcome is measured by the Glasgow Outcome Scale Extended (GOS-E) and the modified Rankin Scale (mRS). A GOS-E score of 1–4 is defined as an unfavourable outcome; 5–8 as a favourable outcome. On the mRS 5-level scale, scores at 3 or below are defined as a favourable outcome; above 3 as an unfavourable outcome. Scores are recorded if stated in the medical record but are otherwise calculated based on records from doctors and physiotherapists, using a standardised calculator from ‘Medscape.com’. If there is no available data follow-up at 30, 60 or 90 days, the closest dates of records are used to calculate GOS-E and mRS scores.
5. Mortality.
6. EVD survival, defined as time from insertion until occurrence of EVD occlusion, resulting in intervention, defined as either flushing, manipulation or catheter replacement.
7. Length of stay defined as length of total hospital admission (days) including ICU admission (days).
8. Procedure costs, defined as costs of EVD surgery.
9. Procedure length, defined as duration of EVD surgery (min).

Risk factors

10. Diagnosis: primary IVH, secondary IVH, ICH or secondary IVH, subarachnoid haemorrhage.
11. Charlson Comorbidity Index (CCI) is used to predict death for patients with specific comorbidities: age, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident

or transient ischaemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, solid tumour, leukaemia, lymphoma and AIDS.

12. EVD type:
 - a. Coating: antibiotic, silver, uncoated or other.
 - b. Size: 8 French or 10 French.
 - c. Fixation method: bolt fixation or tunnelling.
13. EVD treatment data defined as:
 - a. EVD treatment duration.
 - b. Side of EVD placement: Unilateral or bilateral.
 - c. EVD position relative to IVH: in haematoma or in CSF
 - d. CSF leakage from or close to the EVD.
 - e. Number of EVD replacements per patient and per EVD
 - f. Number of flush procedures per patient and per EVD.
14. Haematoma size and distribution:
 - a. Haematoma size at inclusion and during admission
 - b. Graeb score at inclusion
 - c. Ventricular casting.

Research questions and hypotheses

Main research questions associated with EVD complications

- ▶ What is the rate of ventriculitis in EVD-treated patients with IVH?
- ▶ What is the rate of EVD occlusion in patients with IVH?
- ▶ What is the rate of surgical complications in EVD-treated patients with IVH?

Additional research questions

- ▶ What are the functional outcomes in EVD-treated patients with IVH?
- ▶ What is the rate of shunt dependency in EVD-treated patients with IVH?
- ▶ What is the duration of a functional EVD before a complication occurs?
- ▶ What are the financial costs of EVD treatment?

Potential hypotheses for the predictive risk factors associated with EVD complications

- ▶ The risk of CNS infection is associated with EVD type, size, fixation method, duration, placement relative to IVH, replacements, revisions, intraventricular fibrinolysis (IVF) usage, CCI, CSF leakage, as well as the patient’s smoking and alcohol status.
- ▶ The risk of EVD occlusion is associated with the diagnosis, IVF usage, CNS infection, haematoma size, location, Graeb score, ventricular casting, EVD type, size, fixation method, duration, placement relative to IVH, replacements and revisions as well as the patient’s smoking and alcohol status.
- ▶ The risk of surgical complications is associated with the diagnosis, IVF usage, CCI, age, sex, CNS infections, EVD type, size, fixation method,



- duration, placement relative to IVH, replacements and revisions.
- ▶ The rate of shunt dependency is associated with the diagnosis, GCS at admission, pupil size and reactivity at inclusion, CCI, CSF leakage, haematoma size, location, Graeb score, ventricular casting, EVD type, size, fixation method, duration, placement relative to IVH, replacements, revisions as well as the patient's smoking and alcohol status.
 - ▶ The EVD survival time is associated with the diagnosis, CSF leakage, haematoma size, location, Graeb score, ventricular casting, age, sex, IVF usage, EVD type, size, fixation method, duration, placement relative to IVH, replacements, revisions as well as the patient's smoking and alcohol status.
 - ▶ The rate of revision is associated with the diagnosis, IVF usage, CSF leakage, haematoma size, location, Graeb score, ventricular casting, EVD type, size, fixation method, duration, placement relative to IVH, replacements, revisions as well as the patient's smoking and alcohol status.
 - ▶ The functional outcome is associated with the diagnosis, GCS at admission, pupil size and reactivity at inclusion, CCI, CNS infection, haematoma size, location, Graeb score, ventricular casting, EVD type, size, fixation method, duration, placement relative to IVH, replacements, revisions as well as the patient's smoking and alcohol status.
 - ▶ Mortality is associated with the diagnosis, GCS at admission, pupil size and reactivity at inclusion, CCI, CSF leakage, haematoma size, location, Graeb score, ventricular casting, CNS infection, shunt dependency, EVD type, size, fixation method, duration, placement relative to IVH, replacements, revisions as well as the patient's smoking and alcohol status.
 - ▶ The length of hospital stay is associated with diagnosis, GCS at admission, pupil size and reactivity at inclusion, CCI, CNS infection, IVF usage, haematoma size, location, Graeb score, ventricular casting, EVD type, size, fixation method, duration, placement relative to IVH, replacements, revisions as well as the patient's smoking and alcohol status.
 - ▶ EVD surgery costs and duration are not associated with any predefined risk factors in this study.

Data analysis

Descriptive analysis

Study data will be presented as proportions for categorical variables and median with IQRs for continuous variables. Infection-related complications and occlusion rates will be calculated as incidence, incidence per 1000 EVD days and rate per EVD, including s. The incidence rate per 1000 catheter days for catheter-related infections is calculated based on the assumption that infection only occurs once in each patient. Each patient's time of risk starts at the day of EVD insertion. Positive events will be defined as either culture positive CNS infection or culture positive growth at catheter tip on removal.

Statistical analysis

Time-to-occlusion will be analysed with time-to-event methods and Kaplan-Meier plots. Every new occlusion will correspond to a separate sampling unit and each observed time-to-occlusion will be treated as single-record and single-failure survival data. For partial or complete occlusions resolved by either flushing, manipulation or catheter replacement, a new data entry will be used, even if the catheter was not replaced. Since catheter occlusion is independent of patient mortality, patient death is considered a censoring event. Time-to-occlusion will be described by Kaplan-Meier plots. Complications from all sampling units can be investigated by using Cox-regression. Robust variance estimators are used to manage clustering.

Logistic regression will be used to analyse multiple risk factors for binary outcomes, such as risk of CNS infection, risk of EVD occlusion, risk of surgical complication, mortality and functional outcome. Likelihood-ratio tests will also be applied for a fitted model.

For continuous variables with death as competing risk, such as length of ICU stay, length of hospital stay and EVD treatment duration, we consider using a Fine-Gray subdistribution hazard model to estimate the incidence of outcomes over time in case of competing risks.

For other continuous variables, such as rate of shunt dependency and rate of EVD revisions, multiple linear regression will be applied.

Mortality rate and overall survival are calculated using the Kaplan-Meier estimator, patient data are right-censored after the date of medical record collection.

Except for outcome scores, all missing data will be categorised as missing at random and analysis will be based on this assumption. The study protocol requires a 30-day follow-up score for each patient, as discharge records are available. Most patients are expected to need further medical follow-up or rehabilitation, but there may be missing data for the 60-day and 90-day outcome scores. By using repeated measurements, it is possible to use a mixed model to determine whether outcome scores are random or reflected in earlier outcome scores.

All statistical analyses will be performed in RStudio (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.)

Ethics and dissemination

Ethical considerations and data collection

This study is approved by the Central Denmark Region Committee on Health Research Ethics and follows relevant Danish legislation for registry-based research, including the Danish Data Protection Act and the EU General Data Protection Regulation (GDPR). Clinical data and covariates are entered into REDCap hosted by AU. All patient records are securely stored and patient data access will be restricted to the research team.

Dissemination

The results of the study will be presented by the research lead internally at Aarhus University Hospital, at national meetings and congresses in Denmark and possibly as a poster presentation at an international clinical neurosurgery meeting. Data will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and results submitted for publication in a peer-reviewed journal.

Limitations and bias

Patients eligible for inclusion will be identified automatically with procedural and treatment codes. The data accuracy will depend on whether codes are registered correctly. Data will be entered manually in the database following review of patient medical records, which carries a risk of typing errors and false data entries. Some variables from the medical records are converted into scores (eg, GOS-E and mRS), which may enable personal interpretation. However, use of a standardised calculator minimises this risk. REDCap was used in a pilot study and has since then been updated and approved by members of the team, thus limiting design bias.

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