Scandinavian Multicenter Acute Subdural Hematoma (SMASH) Study: Study Protocol for a Multinational Population-Based Consecutive Cohort

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BACKGROUND: Traumatic acute subdural hematomas (ASDHs) are associated with high rate of morbidity and mortality, especially in elderly individuals. However, recent reports indicate that the morbidity and mortality rates might have improved.

OBJECTIVE: To evaluate postoperative (30-d) mortality in younger vs elderly (≥70 yr) patients with ASDH. Comparing younger and elderly patients, the secondary objectives are morbidity patterns of care and 6 mo outcome according to Glasgow outcome scale (GOS). Finally, in patients with traumatic ASDH, we aim to provide prognostic variables.

METHODS: This is a large-scale population-based Scandinavian study including all neurosurgical departments in Denmark and Sweden. All adult (≥18 yr) patients surgically treated between 2010 and 2014 for a traumatic ASDH in Denmark and Sweden will be included. Identification at clinicaltrials.gov is NCT03284190.

EXPECTED OUTCOMES: We expect to provide data on potential differences between younger vs elderly patients in terms of mortality and morbidity. We hypothesize that elderly patients selected for surgery have a similar pattern of care as compared with younger patients. We will provide functional outcome in terms of GOS at 6 mo in younger vs elderly patients undergoing ASDH evacuation. Finally, clinical useful prognostic factors for favorable (GOS 4-5) vs unfavorable (GOS 1-3) will be identified.

DISCUSSION: An improved understanding of the clinical outcome, treatment and resource allocation, clinical course, and the prognostic factors of traumatic ASDH will allow neurosurgeons to make better treatment decisions.

KEY WORDS: Acute subdural hematoma, Outcome, Elderly, Predictors

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GENERAL INFORMATION

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ABBREVIATIONS: ASDH, acute subdural hematoma; **SDH,** subdural hematoma; **CRF,** case report form; **GCS,** Glasgow Coma Scale; **GOS,** Glasgow outcome scale; **ICP,** intrcranial pressure; **SAH,** subarachnoid hemorrhage; **STROBE,** STrengthening the Reporting of OBservational studies in Epidemiology

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RATIONALE AND BACKGROUND INFORMATION

A subdural hematoma is a collection of blood outside the brain between the dura mater and arachnoid mater. It is often due to impact to the skull, causing the brain tissue to accelerate relative to the fixed dural structures, tearing the bridging veins. In other cases, direct injury to the cortical vessels can cause the bleeding. The trauma mechanism varies among patient groups. For younger adults, traffic accidents account for a major number of the injuries, whereas falls at ground level are responsible for most of the injuries in the elderly population.[1] Also, with an aging and more active population, the risk to older individuals of being affected by acute subdural hematoma (ASDH) is increasing. The bleeding and increased pressure on the brain from the subdural hematoma is a life-threatening condition, which often requires emergent surgical evacuation of the hematoma. Secondary reduction in blood-flow and ischemia is also described to be a part of the pathophysiological response. Furthermore, patients presenting with ASDHs often have associated intracranial injuries such as contusion and subarachnoid hemorrhage (SAH), which contribute to the poor prognosis.

Even if surgically treated, ASDHs are related to a high mortality rate, previously described ranging from 40% to 90%.[2,3] However, most the data available are from studies conducted before the 1990s. Recent studies indicate that the mortality rate might have dropped markedly since then, describing mortality rates of 22% to 41%.[4-6]

An ongoing discussion exists on whether or when to perform surgery on elderly patients with traumatic ASDH.[7-11] The evidence clinicians can rely on is unfortunately restricted by the small number of relevant studies. There is a limited number of suggested prognostic factors influencing clinical outcome, including time from trauma to treatment, pupillary abnormalities, neurological presentation, and various computed tomography-findings (hematoma volume, degree of midline-shift, associated intradural lesions, and compressed basal cisterns).[7,12-14] In addition, some studies find advanced age to be an independent factor predicting poor outcome,[8-11] while other fail to do so.[3] Consequently, the treatment of elderly patients suffering from ASDH remains controversial. Meanwhile, marked improvements have been seen in the treatment of traumatic brain injuries, including rapid prehospital stabilization and transportation, specialized trauma centers, intensive care unit management, and improved surgical techniques.[3,11,15]

With this study, we want to compare the clinical course and clinical outcome of elderly patients (≥70 yr old) compared with younger patients (<70 yr old) with ASDHs treated surgically. An improved understanding of the clinical outcome, clinical course, and the prognostic factors of ASDHs would allow physicians to make better decisions about treatment options in traumatic ASDH in the elderly population.

STUDY GOALS AND OBJECTIVES

The primary objective is to evaluate 30-d mortality (perioperative death) in younger vs elderly (≥70 yr) patients with ASDH. The secondary objectives are to:

a) Describe pattern of care in younger vs the elderly.
b) Describe clinical outcome—Glasgow outcome scale (GOS) at 6-mo (range, 3-12) follow-up in younger vs elderly (≥70 yr) patients:

- Favorable outcome predefined as GOS 4 to 5
- Unfavorable outcome predefined as GOS 1 to 3

c) 30-d morbidity (according to the Ibanez classification[16]) in younger vs elderly (≥70 yr) patients.
d) To assess the effect of age as an independent prognostic factor in traumatic ASDH for outcome (GOS) in the elderly (≥70 yr) using a 3-step approach:

- Match elderly (cases) with younger (controls) patients with respect to Glasgow Coma Scale (GCS) at admission to treating hospital (categories: mild [GCS 14-15], moderate [GCS 9-13], severe [GCS 3-8]), midline-shift (with a cut off >10 mm), dilated pupil(s) (yes/no)
- Using a multivariable approach with all patients including age (continuous variable) to identify independent predictors of an unfavorable outcome (GOS 1-3)
- Using a multivariable approach including age as a continuous variable within the elderly population (≥70 yr) to identify independent predictors of an unfavorable outcome among the oldest (GOS 1-3)

STUDY DESIGN

The study is a retrospective, population-based, Scandinavian observational study. The protocol was designed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines, with study results to be reported according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

METHODOLOGY

All patients treated with craniotomy for traumatic ASDH (ICD-10 S06.5 code) will be identified in the surgery protocols at the respective hospitals. Baseline factors (patient demographics, clinical and imaging data) and outcome data will be collected from the electronic health journals, anonymized, and written into a predefined CRF (case report form, **Supplemental Digital Content**). Upon completion, data will be analyzed according to

the predefined statistical analysis aiming at answering the primary and secondary aims of this study.

Scandinavian Health Care System and Person Identification System

The health care system in Denmark and Sweden is divided into different geographical regions with compliant referral patterns for intracranial surgery within these regions. Nevertheless, any cross-over does not alter the population-based setting since all centers involved in ASDH treatment in Denmark and Sweden are included. Citizens of Denmark and Sweden are equipped with a unique personal identification number, and even if treated at one center and receiving follow-up at another center patients are traceable, ensuring minimal loss to follow-up due to nationwide collaboration.

Subjects

Inclusion Criteria

Adult (≥18 yr old) patients surgically treated with craniotomy for a traumatic ASDH in the period January 1, 2010 to December 31, 2014 at one of the participating centers were included.

Exclusion Criteria

Patients diagnosed with nontraumatic ASDH (ie, spontaneous or postoperative) will be excluded, as will those with a permanent intracranial device (ie, deep brain stimulation electrode or ventriculoperitoneal shunt) and those who had intracranial surgery performed within 6 mo prior to the trauma. Patients with permanent residency outside Denmark or Sweden (ie, tourists) were also excluded.

Study Description

The data reporting will be based on the STROBE guidelines, with data collection according to attached CRF protocol (see **Supplemental Digital Content** for the CRF with a complete list of variables).

In brief, demographic variables such as patient age, gender, premorbid level of independence, co-morbidity according to Charlson et al[17] (1), premorbid anticoagulation/antiplatelet therapy, but also timeline relevant data such as date of trauma, data of admission to treating hospital, and date of surgery. Baseline data also encompass clinical and imaging data, including biochemistry (coagulation status tests), trauma-related variables such as trauma mechanism, as well as energy level. Also, a detailed description of the patient's status upon hospital admission including, ie the GCS, pupillary response, Injury Severity Score (2), and treatment to lower intrcranial pressure (ICP; ie mannitol, hyperventialation, hypertonic saline) before surgery will be registered.

Data related to the surgery will include the type of procedure performed (craniotomy with or without additional intradural ICP lowering treatment, ie, hemicraniectomy) and if ICP monitoring has been implemented or not. Also, all later surgical interventions (ie, hematoma recurrence and reoperation, ventricular drain placement etc) will be registered.

Diagnostic imaging will include a detailed description of the ASDH (morphology), in combination with description of any other abnormal findings (ie, traumatic SAH, contusions), as well as an estimate of the hematoma volume according to the formula: (length cm × width cm × height cm)/2 (3). Further, diffuse traumatic axonal injury score (4) and the Rotterdam traumatic brain injury (TBI) score (5) will be assessed.

Outcome assessment includes 30-d morbidity according to Ibanez et al[16] (6), length of ventilator treatment, presence of epilepsy, GOS at 6-mo follow-up, and 1-yr mortality.

DISCUSSION

While no clinician would argue against neurosurgical intervention in younger individuals in a reasonable clinical state with an ASDH, the same physician might hesitate in case of an elderly patient with multiple comorbidities. The question of when to proceed with surgery, and when not to in elderly patients with ASDH, has also been sought to be answered previously. Thus far, treatment is mainly based on studies performed in the 80 to 90s, with mortality rate ranging 74% to 88% in elderly patients with ASDH,[10,18-20] and good outcome only reported in 18%.[21] While newer studies exist,[22] these are often single institution series with small sample size with the risk of selection bias and local treatment policies affecting the results. Further, to maximize inclusion, some case series are spanning several decades without considering medical advances (eg, intensive care therapy) taking place during the course of the study period.[21] Meanwhile, during the past decades, the median age of patient with TBI has increased from 25 to 55 yr, presumably increasing even more in the future.[23,24] And while delayed burr hole drainage of the subdural hematoma (SDH) after evolution to a chronic SDH remains a mainstay treatment in the elderly patients who can tolerate a delay in treatment, our study focus on the patients that could not tolerate a delay in treatment, and need a craniotomy on an emergency basis for an ASDH.

To take advantage of the Scandinavian population-based catchment area system, eliminating referral bias, and the homogenous treatment algorithms across Scandinavian centers, based on joint residence training courses (https://www.ous-research.no/langmoen/) and common guidelines published through the Scandinavian neurotrauma committee (http://www.neurotrauma.nu/). This provides a unique environment for Scandinavian multicenter studies.

A large population-based Scandinavian study of ASDH patients well-characterized in terms of baseline demographics, treatment, as well as outcome, is well-suited to explore multiple endpoints while still adhering to the STROBE guidelines and avoiding data mining by rigid protocol adherence and endpoint definition before initiation of data collection. Although it is difficult to establish causality from observational studies, a larger

study with adjustment for potential confounding factors could allow for a better estimation of effect size than both small underpowered RCTs and small cohort studies.

Limitations

Limitations inherent to retrospective assessment are present in this study. However, the relevance of mortality and morbidity rates in surgically treated elderly patients remains indisputable. The major strengths of this study are the large sample size in combination with homogenous treatment selection, population-based approach, and low rates of missing data.

TRIAL STATUS

At the time of manuscript submission, the data gathering have been initiated at all sites.

FOLLOW-UP

Follow-up will include: length of ventilator treatment (days), 30-d (peroperative) mortality and risk of adverse events (according to Ibanez et al[16]), visit in the outpatient clinic in order to estimate GOS closest to 6 mo after surgery (range, 3-12 mo), 1-yr risk of epilepsy (y/n), and 1-yr mortality (y/n).

DATA MANAGEMENT AND STATISTICAL ANALYSIS

The statistical analysis will be performed with the help of a biostatistician according to the following analytic plan: statistical significance level is set to $P < .05$. Q-Q plots will be used to test for normal distribution of data. Where data are normally distributed central tendencies will be presented as means ± SD. Central tendencies will be presented as medians and interquartile range if data are skewed. Primary outcome will be assessed using chi-square analysis, and similar method will also be used for analyses of secondary outcomes morbidity and favorable outcome (GOS 4-5). Patterns of care will be described in a descriptive fashion, however, using chi-square test for single parameters (eg, ICP monitor, yes or no). The multivariable models created will use known clinical factors importance forced into the model, in addition to a forward step-wise selection of other potential predictive variables.

QUALITY ASSURANCE

Data quality assurance will be undertaken by cross-monitoring and random data quality control in-between centers. Dr Jiri Bartek Jr is the guarantor of data completeness and accuracy.

EXPECTED OUTCOMES OF THE STUDY

We expect there to be no major difference between younger vs elderly patients in terms of mortality and morbidity. We hypothesize that elderly patients selected for surgery have a similar pattern of care as compared with younger patients. GOS at 6 mo is expected to be similar in younger vs elderly patients undergoing ASDH evacuation. Finally, clinical useful prognostic factors for favorable (GOS 4-5) vs unfavorable (GOS 1-3) will be identified.

DURATION OF THE PROJECT

We anticipate the data gathering to be complete by the spring/summer of 2018, with data analysis performed during the fall of 2018.

PROJECT MANAGEMENT

The principal investigator, Dr Jiri Bartek Jr, planned the study and is the project leader. Dr Asgeir Store Jakola will be responsible for overall data management and analyses. At each site, the respective co-authors are responsible for data collection according to a standardized CRF created by Jiri Bartek Jr and Asgeir S. Jakola. The interpretation of the data and writing of the manuscript will be done by all authors.

ETHICS

An approval from the Danish Medical Agency (J.nr. 3-3013-1218/1) has been obtained together with permission from the data protection agency (J.nr. 2012-58-0004) in Denmark. No ethical approval is necessary for this retrospective observational study in Denmark. In Sweden, ethical approval has been obtained (D-nr 2016/1499-31/4). Due to the retrospective nature of this study, the need for written consent has been waived by the respective authorities in both Denmark and Sweden.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content. Case Report Form to be filled out for each study participant.

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