Loss of Consciousness at Onset of Aneurysmal Subarachnoid Hemorrhage is Associated with Functional Outcomes in Good-Grade Patients

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■ BACKGROUND: **Transient loss of consciousness (LOC) is one of the most common presentations of aneurysmal subarachnoid hemorrhage (SAH) and may be an indicator of early brain injury. In this study, we examined the association of LOC and functional outcomes in patients with good-grade SAH.**

■ METHODS: **We searched the Subarachnoid Hemorrhage International Trialists Repository for patients who presented with LOC at ictus of SAH. A propensity score analysis was performed on good-grade patients (defined as World Federation of Neurosurgical Societies grade 1–3) to balance selected covariates between those with and without LOC. The primary outcome was Glasgow Outcome Score (GOS) at 3 months (with poor outcome defined as a GOS of 1–3). Secondary outcomes were delayed cerebral ischemia (DCI), rebleed, length of hospital stay, and time to death.**

■ RESULTS: **A propensity score-matching algorithm identified 336 patients (168 with and 168 without LOC at ictus). The proportion of patients with poor functional outcome at 3 months was significantly higher in the cohort with LOC at ictus compared with the matched cohort without LOC at ictus (30% vs. 19%; $P = 0.02$). There was a nonsignificant trend toward greater mortality in the patients with LOC at ictus (19% vs. 13%; $P = 0.14$). There were no significant differences in the secondary outcomes between the 2 cohorts.**

■ CONCLUSIONS: **LOC at ictus of SAH is associated with a higher rate of unfavorable functional outcomes but not of mortality, DCI, or rebleed in patients with good-grade SAH. Future studies should further investigate the putative mechanisms through which LOC mediates early brain injury in SAH.**

INTRODUCTION

Intracranial aneurysmal rupture, the most common cause of nontraumatic subarachnoid hemorrhage (SAH), carries a mortality rate as high as 67% in the first few months after rupture.[1] A significant proportion of the patients who do survive are left with significant disability and loss of independence. Almost 30% of survivors have moderate to severe disabilities afterward, and approximately 65% never return to the same quality of life that they enjoyed before SAH.[2] Prognostication in SAH is essential, influencing clinical decisions on initial management, monitoring, and duration of stay in the intensive care unit. Known prognostic factors associated with worse outcome include, but are not limited, to increasing patient age, worsening neurologic grade, ruptured posterior circulation

Key words
- Loss of consciousness
- Subarachnoid hemorrhage

Abbreviations and Acronyms
BRANT: British Aneurysm Nimodipine Trial
CI: Confidence interval
CPP: Cerebral perfusion pressure
DCI: Delayed cerebral ischemia
GOS: Glasgow Outcome Scale
H&H: Hunt and Hess
ICP: Intracranial pressure
LOC: Loss of consciousness
OR: Odds ratio
SAH: Subarachnoid hemorrhage
SAHIT: Subarachnoid Hemorrhage International Trialists
WFNS: World Federation of Neurosurgical Societies

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**A list of the SAHIT collaborators is presented in the Appendix.*

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aneurysm, larger aneurysm size, more subarachnoid blood detected radiographically, presence of intraventricular and/or intracerebral hemorrhage, and presence of comorbidities, including hypertension, myocardial infarction, liver disease, or previous SAH.[3,4]

Loss of consciousness (LOC) is one of the most common presenting symptoms in aneurysmal SAH and has been associated with worse clinical grade, larger hemorrhages, global cerebral edema, poor outcomes, and delayed cerebral ischemia (DCI).[5-8] The largest study of LOC in SAH was reported in 2016 by Suwatcharangkoon et al.,[6] who retrospectively analyzed a prospective series of 1460 patients with spontaneous SAH. An important question that arose was in regard to how to separate the effect of LOC from the patient's presenting neurologic grade, using the Hunt and Hess (H&H) or World Federation of Neurosurgical Societies (WFNS) grading system.[5] Since high-grade patients (H&H 4–5; WFNS 4–5) have LOC by definition, it may be of value to assess LOC in otherwise low-grade patients to better assess its contribution to outcome after aneurysmal SAH. This is also of particular importance in determining the association between LOC and DCI following SAH.

Therefore, we aimed to examine the prognostic significance of LOC in patients with SAH, particularly in patients with good neurologic grade in terms of functional outcome, mortality, and SAH-associated complications, including DCI.

METHODS

Study and Patient Selection

We conducted our data search using the Subarachnoid Hemorrhage International Trialists (SAHIT) Repository, a combined database of recent clinical trials and prospective patient data from institutions worldwide on the topic of aneurysmal SAH.[9,10] The SAHIT Repository has provided data for a number of previous studies of SAH.[9-14] Our search included all studies in the repository. Our inclusion criteria were as follows: 1) good neurologic grade on admission, defined as a WFNS or H&H grade 1–3; 2) the presence or absence of LOC at ictus; and 3) data on functional outcomes, as evaluated with the modified Rankin Scale, Glasgow outcome scale (GOS), and/or extended GOS at different serial time points.[15]

Because poor neurologic grade, defined as WFNS or H&H grade 4–5, is a strong predictor of poor outcome, this acts as a notable confounder when attempting to evaluate the role of LOC as an independent prognostic factor.[5,16] Furthermore, patients with a poor neurologic grade are often unconscious by definition. A poor neurologic grade is a one-time designation assigned to patients on presentation, whereas LOC, depending on how it is defined, can occur before admission and at any time after initial presentation to the hospital. Therefore, to control for this, we limited our analysis to patients with a good neurologic grade on presentation as defined above.[17-21]

Only one dataset was eligible for our study in terms of meeting our foregoing inclusion criteria. This dataset was from the British Aneurysm Nimodipine Trial (BRANT), a double-blind, placebo-controlled randomized trial of the effect of nimodipine in the prevention of DCI reported by Pickard et al.[22] The BRANT remains one of the most highly cited works on aneurysmal SAH and has provided the basis for the current use of nimodipine post-SAH as the standard of care.[23] Details of the BRANT are summarized below.

Clinical Assessment

A post hoc analysis was performed on the 554 patients enrolled in the BRANT, recruited from 4 neurosurgical units in the United Kingdom. A total of 1115 patients were initially admitted to participating centers between June 1985 and September 1987 with SAH diagnosed by lumbar puncture or computed tomography scan. Patients who presented more than 96 hours after SAH were excluded. Other exclusion criteria were pregnancy; major renal, hepatic, or pulmonary disease; preexisting cardiac decompensation; myocardial infarction within the previous 6 months; age <18 years; prior SAH in the previous week resulting in coma; and inability to obtain consent. Eligible patients were assigned a WFNS neurologic grade and were randomized to receive either placebo or 60 mg of nimodipine every 4 hours for 21 days. Study endpoints were incidence of cerebral infarction, ischemic neurologic deficits, and outcome at 3 months after enrollment.[22] LOC in the BRANT-SAHIT dataset was broadly defined as occurrence of unresponsiveness at the onset of SAH.

Outcomes

The primary outcome for our post hoc analysis was the 5-point GOS as a measure of functional outcome, with a score of 1–3 designated as unfavorable (i.e., death, vegetative state, and severe disability precluding the ability to live independently, respectively).[22] Outcome assessment at the 3-month follow-up was conducted in person by a physician not involved in the patient's initial early management or through mail or telephone interview if a patient was directly unavailable or had relocated out of the region.

Secondary outcomes were DCI, time to DCI, aneurysmal rebleed, length of hospital stay, and time to death. Rebleed or DCI in the trial was categorized as either "definitive" if confirmatory evidence of a bleed or infarct was present on computed tomography scan, during surgery, or during autopsy, or "probable" if based solely on clinical factors and suspicion. For our analysis, only definitive evidence of DCI and rebleed were included.

Statistical Analysis

For analysis, we used a propensity score-matching algorithm with LOC at the ictus of SAH as the dichotomous exposure cohort. Covariates balanced between the 2 cohorts (LOC present vs. absent at ictus) included age, sex, history of hypertension, history of cardiac disease, WFNS grade, motor deficits, hypertension at admission (defined as systolic blood pressure ≥140/90 mmHg), treatment cohort (placebo vs. nimodipine), and time from SAH to aneurysm surgery. We used caliper matching in our analysis, with caliper width equal to 0.25 times the standard deviation of the logit of the propensity score, with a 1:1 match ratio between the LOC present and LOC absent cohorts. Previous work by Austin has shown that calipers of a width close to 0.2 minimizes the mean squared error of the estimated treatment effect and eliminates bias in the estimator to produce confidence intervals (CIs) with the appropriate coverage rates.[24] Balance between the covariates in the 2 cohorts used in matching was assessed by plotting propensity