Seizures After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review of Outcomes

Daniel M. S. Raper[1], Robert M. Starke[2], Ricardo J. Komotar[3], Rodney Allan[4], E. Sander Connolly, Jr.[5]

Key words
- Aneurysm
- Endovascular
- Intracranial
- Microsurgery
- Seizure

Abbreviations and Acronyms
ACA: Anterior cerebral artery
ACommA: Anterior communicating artery
AED: Antiepileptic drug
aSAH: Aneurysmal subarachnoid hemorrhage
HH: Hunt and Hess
ISAT: International Subarachnoid Aneurysm trial
MCA: Middle cerebral artery
SAH: Subarachnoid hemorrhage

From the [1]Royal North Shore Hospital, Sydney, New South Wales, Australia; [2]Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, USA; [3]Department of Neurological Surgery, University of Miami, Miami, Florida, USA; [4]Department of Neurosurgery, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia; and [5]Department of Neurological Surgery, Columbia University, New York, New York, USA

To whom correspondence should be addressed: Daniel M. S. Raper, M.B.B.S. [E-mail: drap7157@uni.sydney.edu.au]

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OBJECTIVE: **The risk for early and late seizures after aneurysmal subarachnoid hemorrhage (aSAH), as well as the effect of antiepileptic drug (AED) prophylaxis and the influence of treatment modality, remain unclear. We conducted a systematic review of case series and randomized trials in the hope of furthering our understanding of the risk of seizures after aSAH and the effect of AED prophylaxis and surgical clipping or endovascular coiling on this important adverse outcome.**

METHODS: **We performed a MEDLINE (1985–2011) search to identify randomized controlled trials and retrospective series of aSAH. Statistical analyses of categorical variables such as presentation and early and late seizures were carried out using χ^2 and Fisher exact tests.**

RESULTS: **We included 25 studies involving 7002 patients. The rate of early postoperative seizure was 2.3%. The rate of late postoperative seizure was 5.5%. The average time to late seizure was 7.45 months. Patients who experienced a late seizure were more likely to have MCA aneurysms, be Hunt/Hess grade III, and be repaired with microsurgical clipping than endovascular coiling.**

CONCLUSIONS: **Despite improved microsurgical techniques and antiepileptic drug prophylaxis, a significant proportion of patients undergoing aneurysm clipping still experience seizures. Seizures may occur years after aneurysm repair, and careful monitoring for late complications remains important. Furthermore, routine perioperative AED use does not seem to prevent seizures after SAH.**

INTRODUCTION

Seizures are a well-recognized complication after aneurysmal subarachnoid hemorrhage (aSAH), and have been correlated with higher aneurysm grade, lower Glasgow Coma Scale score at presentation, extent of subarachnoid blood on computed tomography, and rebleeding (2, 18, 29, 40, 53). Early studies reported seizures in over 10% of survivors of aSAH; these were more likely in younger patients, those with middle cerebral artery (MCA) aneurysms, and those with coexisting intracerebral hemorrhage (11, 46). Seizures have been observed after both microsurgical clipping and endovascular coiling (9, 13). In the International Subarachnoid Aneurysm trial (ISAT) and subsequent subgroup analyses, patients treated with clipping had a significantly higher risk of late seizure than those treated with coiling (32, 42, 49). Nevertheless, the influence of treatment modality on either early or late seizure outcomes has not been assessed in a systematic review of the literature.

The administration of prophylactic antiepileptic drugs (AEDs) has in the past been a standard protocol for patients undergoing many neurosurgical procedures. More recently, however, routine use of AEDs for aSAH patients has come under question (45). Low seizure rates have been reported in series of patients with aSAH (9, 11). In reviewing these and other modern experiences, the Stroke Council of America guidelines, published in 2009, recommended against routine perioperative AED use in ruptured aneurysms because of a paucity of evidence of benefit (4). Furthermore phenytoin, which has traditionally been the most commonly used AED for aneurysm patients, has a variety of adverse effects and has been correlated with poor functional outcomes and cognitive status after subarachnoid hemorrhage (SAH) (33). Nevertheless, in a 2002 survey conducted by the American Association of Neurological Surgeons, 24% of neurosurgeons surveyed routinely prescribed AEDs for 3 months after SAH regardless of whether seizures occurred at presentation, in hospital, or not at all (3, 13, 17, 18). The use of AEDs as a primary prophylactic measure in aSAH patients thus remains controversial.

In order to gain a better understanding of the risk for early and late seizures after aSAH, and to provide a quantitative supplementation to recent consensus statements on the topic (26), we believe it useful to survey the modern published literature. To

this end, we have performed a systematic review of the available published reports of outcomes following aneurysm repair after SAH in order to gain a more comprehensive assessment of the risk of seizure and the influence of AED prophylaxis and treatment modality.

MATERIALS AND METHODS

Study Selection

We performed a modern literature search using the Ovid gateway of the MEDLINE database between the years 1985 and 2010. The following key words were queried singly and/or in combination: seizure, subarachnoid, hemorrhage, epilepsy, aneurysm, antiepileptic, anticonvulsant, outcome, surgery. The search was limited to studies published in English, and humans were specified as the study category. No specific review protocol was used for this systematic review.

Eligibility criteria were limited by the nature of existing literature on this topic, which consists largely of retrospective case series. To gain a more accurate reflection of seizure incidence using modern microsurgical and endovascular techniques, only reports published after 1985 were included in this review. All publications reporting seizure outcomes after surgery or endovascular intervention for ruptured intracranial aneurysms were selected, whereas editorials, commentaries, and review articles were not, because they did not include original data. Series that included patients with unruptured aneurysms or patients with a past history of epilepsy were also excluded from this analysis. To avoid duplication of patients, in cases in which multiple articles were published from the same authors or the same institution, only the report with the largest relevant cohort was included. A manual search for manuscripts was also conducted by scrutinizing references from identified manuscripts, major neurosurgical journals and texts, and personal files. The date of the last search was March 2011.

Data Extraction

Included studies were reviewed and carefully scrutinized for study design, methodology, and patient characteristics. The total number of patients for each study was extracted and divided into cohorts according to aneurysm location and treatment strategy. Data for all patients were recorded when available, including mean age, sex, aneurysm location, presentation seizure, and SAH grade. Presentation seizures were defined as those occurring before the first intervention for SAH. Early seizures were defined as those that occurred after intervention during the initial hospital stay. Late seizures were defined as those that occurred after discharge from hospital. Because the series in this review included randomized trials as well as prospective and retrospective case series, an assessment of bias was made only on the outcome level rather than at the individual study level. The interpretation of these results is limited by this unquantified level of bias, and makes our systematic review a synthesis of level 3 evidence only.

Statistical Analysis and Systematic Analysis

Data from the individual studies were combined by cohort and then compared. Statistical analyses of categorical variables were carried out using χ^2 and Fisher exact tests as appropriate. Because there were significant differences between cohorts, analysis of heterogeneity was not carried out. Values of $P \leq .05$ were considered statistically significant.

RESULTS

Study Selection and Study Characteristics

A total of 87 published studies since 1985 were identified through our initial MEDLINE database search. After removal of duplicates, all records were screened by review of abstracts for suitability. The full text of all records with reference to aneurysm and seizure was downloaded and filtered for mention of seizure outcomes using a combination of search terms (epilep*, seiz*, convul*, etc.) Applicable records were thoroughly reviewed for final inclusion or exclusion. Altogether, 62 records were rejected from our review because they did not include original data, did not report seizure outcomes, or did not differentiate between ruptured and unruptured aneurysms. Studies were analyzed with respect to overall seizure outcomes, as well as seizure outcomes between cohorts that received AED prophylaxis vs. those that received no AED prophylaxis, and between cohorts of aneurysms that were clipped vs. those that were coiled. A total of 25 studies reported seizure outcomes after aSAH. Fourteen studies reported outcomes among cohorts of aSAH patients who received AED prophylaxis (3, 10, 12, 13, 16, 19, 22, 23, 27, 34, 41, 44, 50, 53), 3 studies reported outcomes in those who did not receive AED prophylaxis (6, 7, 39), and 3 studies compared cohorts treated with AED or no AED prophylaxis (28, 38, 43). Fifteen studies reported outcomes among cohorts of aSAH patients who were clipped (3, 6, 7, 10, 16, 19, 22, 23, 27, 30, 34, 39, 40, 53), 1 study reported outcomes in those who were coiled (9), and 3 studies compared cohorts who were clipped and coiled, reporting seizure outcomes (28, 32, 43). A total of 25 studies and 7002 patients were included in this review.

Characteristics and primary findings of the 25 included studies of seizures in patients with aneurysmal SAH are summarized in **Table 1**. Regarding study design, 21 articles were retrospective (3, 7, 9, 10, 12, 16, 19, 22, 23, 27, 28, 34, 38-41, 43, 44, 50, 51, 53), 3 were prospective (13, 16, 30), and there was 1 randomized controlled trial (32).

Patient Characteristics

Patient characteristics of the whole cohort, as well as cohorts of clipped vs. coiled and AED prophylaxis vs. no AED prophylaxis, are reported in **Table 2**. In total there were 7002 patients, mean age 51.3, mean follow-up 46.6 months, 37.5% male. Aneurysms were located most commonly in the anterior communicating artery (ACommA) and MCA, and were evenly split between Hunt and Hess (HH) grades I, II, and III. In the clipped cohort there were 4378 patients, mean age 49.5, mean follow-up 50.9 months, 40.5% male. Aneurysms were located in the anterior circulation in 93.2%, most commonly HH grade II. In the coiled cohort there were 1418 patients, mean age 52.2, mean follow-up 43.0 months, 36.6% male. Aneurysms were located in the anterior circulation in 71.1%; the HH grade was not reported in any reports of coiled aneurysms. The 2 cohorts did not differ significantly in any patient or aneurysm characteristics. In the AED cohort there were 3232