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REVIEW

Seizures and Anticonvulsants after Aneurysmal Subarachnoid Hemorrhage

Giuseppe Lanzino · Pietro Ivo D'Urso · Jose Suarez · The Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage

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Abstract Seizures and seizure-like activity may occur in patients experiencing aneurysmal subarachnoid hemorrhage. Treatment of these events with prophylactic antiepileptic drugs remains controversial. An electronic literature search was conducted for English language articles describing the incidence and treatment of seizures after aneurysmal subarachnoid hemorrhage from 1980 to October 2010. A total of 56 articles were included in this review. Seizures often occur at the time of initial presentation or aneurysmal rebleeding before aneurysm treatment. Seizures occur in about 2% of patients after invasive aneurysm treatment, with a higher incidence after surgical clipping compared with endovascular repair. Non-convulsive seizures should be considered in patients with poor neurological status or deterioration. Seizure prophylaxis with antiepileptic drugs is controversial, with limited data available for developing recommendations. While antiepileptic drug use has been linked to worse prognosis, studies have evaluated treatment with almost exclusively phenytoin. When prophylaxis is used, 3-day treatment seems to provide similar seizure prevention with better outcome compared with longer-term treatment.

Keywords Antiepileptic drug · Epileptiform · Non-convulsive · Phenytoin · Seizure · Tonic

Introduction

Seizures and seizure-like phenomena are not uncommon after aneurysmal subarachnoid hemorrhage (SAH). At the time of the acute presentation, frank tonic/clonic seizures can occur, as well as seizure-like tonic movements related to herniation or increased intracranial pressure [1–8]. Both generalized and focal seizures may also occur during hospitalization for SAH and during follow-up.

The significance of and appropriate treatment for seizures related to SAH are areas of debate. While antiepileptic drugs (AEDs) may be prescribed to prevent seizures and additional neurological injury after SAH, well-designed, randomized, controlled trials to provide solid data to develop evidence-based practice guidelines are lacking. The need for routine antiepileptic drugs treatment after SAH and the appropriate duration of anticonvulsant prophylaxis are controversial; there are limited controlled data supporting benefits as well as the potential for medication-related side effects.

Methods

An electronic literature search was performed of the National Library of Medicine, EBSCO, EMBASE (Ovid), Cochrane Library from 1980 to October 2010 to identify articles

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G. Lanzino (✉) · P. I. D'Urso
Department of Neurologic Surgery, Mayo Clinic, 200 First Street South West, Rochester, MN 55905, USA
e-mail: Lanzino.giuseppe@mayo.edu

J. Suarez
Department of Neurology, Baylor College of Medicine, Houston, TX, USA

addressing the incidence and significance of seizures in patients with SAH and the effect of prophylactic treatment. In press articles that were available to be viewed online prior to the cut-off of October 2010 were also included. Candidate articles were identified by searching titles and abstracts for the key word "subarachnoid hemorrhage" and at least one of the following additional key words: "seizures," "epilepsy," "convulsive status," "non-convulsive status," "convulsion," "antiepileptic drug," "anticonvulsant," "phenytoin," "levetiracetam," or "carbamazepine."

Abstracts for potential selection were screened to see whether they described studies that involved human subjects, and the full manuscript was published in English. Both original research and review articles were included. Studies addressing traumatic SAH were excluded. Selected articles were those that directly addressed the proposed areas of interest (seizure occurrence and AED prophylaxis). Following identification of articles to be included in this review, additional references were identified by reviewing citations provided in the list of references cited in each paper to determine additional studies likely to meet inclusion criteria. Original research studies were evaluated for quality of data and strength of recommendations using the GRADE approach [9].

Summary of the Pertinent Literature

A total of 56 papers were identified for this review. A sample of data from 23 representative original research studies are cataloged in Table 1, which describes study design, outcome, level of research, and balance of potential benefits versus risks [1, 2, 4, 5, 10–28]. In all but one case [18], quality of evidence was very low or low. None of the studies were able to be assigned a recommendation strength, due to insufficient data.

Incidence of Seizures

Seizures occurring at the time of SAH are called onset seizures. The reported incidence of onset seizures varies between 4 and 26% [1–6, 13, 24, 29, 30]. This wide variation in reported events is in part related to the occurrence of seizure-like tonic phenomena related to hyperextension that can occur secondary to herniation or increased intracranial pressure [1–6]. These events may be difficult to distinguish from true seizures. Often, the description of these events is provided by non-medical bystanders with insufficient background to differentiate tonic events from seizures.

Seizures occurring after hospital admission but prior to aneurysm treatment are often a symptom of rebleeding. Data from the International Subarachnoid Aneurysm Trial (ISAT) indicate that pretreatment seizures often herald rebleeding [18]. Among the 2,143 SAH patients included in the ISAT sample, 14 patients (0.65%) suffered seizures after hospitalization but before treatment of the aneurysm. In 9 of these 14 cases, seizure was associated with rebleeding.

Seizure incidence after aneurysm treatment may vary based on treatment. In the ISAT sample, seizures occurred in 2.3% after treatment of the index aneurysm and until discharge [18]. The frequency of seizures after treatment and before discharge was doubled in patients treated with surgical clipping (3%) compared with those receiving endovascular treatment (1.4%) [18]. The difference in seizures frequency between the two treatment modalities was particularly marked in older patients. In a subgroup analysis of 278 patients $>$ 65 years old in the ISAT cohort, seizures occurred in 0.7% of patients treated with coil embolization and in 12.9% of those treated with surgical clipping ($P < 0.001$) [31]. In the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), overall seizure incidence was similar among patients randomly assigned to intraoperative hypothermia (7%) or normothermia (6%) [32]. Seizures beginning $>$ 2 weeks after surgery for SAH treated with aneurysm clipping are uncommon [33].

Seizures occurring during hospitalization have been linked to a variety of disease severity markers, with correlations found with poor neurological status at admission, prolonged loss of consciousness at presentation, middle cerebral artery aneurysm location, higher cisternal clot burden, rebleeding, and the presence of intracerebral hematomas, hydrocephalus, and cerebral ischemia [2, 4, 5, 10, 15, 17, 22, 26, 34–37]. These same risk factors have also been linked with late seizures occurrence [26, 38, 39]. Contrasting data exist about the correlation between in-hospital seizures and poor outcome. In a retrospective analysis of prospectively collected data from 527 patients with SAH, seizures occurring during hospitalization did not correlate with worse outcome [19]. These data suggested that seizures in patients with SAH are an indication of more severe disease rather than being an independent predictor of poorer outcome. Similar data were reported by Lin and coworkers in a retrospective study of 137 patients with SAH [25]. They found that higher-grade SAH on presentation was predictive of seizure, but the presence of seizures itself was not a significant predictor of prognosis after 1-year follow-up. Conversely, other studies have reported that seizures after SAH are associated with poor outcome [1, 40].

During the first year after discharge, the incidence of seizures is approximately 1.3% after endovascular treatment and 2.2% after surgery [18]. The risk of new-onset

Table 1 Summary of the literature data

Authors and year	Methods	Population	Treatment assignment	Findings	Aneurysm treatment	Quality of evidence	Balance of benefit vs. harm
Hasan et al. [10]	RS	381	PHT	Overall epilepsy: 9% Early epilepsy 5% Late epilepsy 3% High cisternal blood and rebleeding related to epilepsy ($P = 0.04$, 0.016), even after exclusion of patients treated with prophylactic AEDs ($P = 0.006$)	Clipping	Low	NA
Baker et al. [11]	RS	398	PTH (94.6%)	Overall seizure rate 5.4% Ruptured Early postoperative seizures 1.5% Late seizures 3.0% UNRUPTURED Early postoperative seizures 2.6% Late seizures 4.4% No statistical association between durations of AEDs and risk of early or late seizures	Clipping	Low	Uncertain trade-offs
Pinto et al. [4]	RS of prospectively collected data	253	PHT	OS: 6.3% LS: 0.3% Hemiparesis, poor clinical grade, Fisher 3–4 predisposing factors for onset seizures ($P < 0.02$) Severe disability more frequent in patients with onset seizures ($P < 0.05$) OS not significant predictor of disability or death	Clipping	Low	NA
Butzkueven et al. [1]	RS	410	No specified	OS 7.8% LS 5.1% OS correlated with the extent of blood on initial CT (OR 1.1, $P = 0.05$) Disability independently predicted by OS ($P = 0.04$) LS independently related to rebleeding (OR 94, $P < 0.01$) and OS (OR 27, $P < 0.01$)	NS	Very low	NA

Table 1 continued

Authors and year	Methods	Population	Treatment assignment	Findings	Aneurysm treatment	Quality of evidence	Balance of benefit vs. harm
Rhoney et al. [5]	RS	95	PHT 64% Carbamazepine 23% Valproic acid 2%	OS 17.9% In-hospital seizures 4.1% Longer hospital stays in patients with seizure (24 vs. 14 days, $P = 0.02$) No differences in GOS AEDs adverse effects 13%	Clipping in 89% of patients	Very low	Uncertain trade-offs
Olafsson et al. [12]	RS	44	Not specified	Actuarial risk for epilepsy: 1 year: 18% 2 years: 23% 5 years: 25% Actuarial risk for epilepsy (pts with OS): 1 year: 60% 2 years: 70% Actuarial risk of epilepsy (pts without OS): 1 year: 6% 2 years: 9% 5 years: 12% Relative risk of epilepsy in patients with onset seizures: 6.0	Clipping	Low	NA
Labovitz et al. [13]	RS	904 strokes; 50 SAH	Not specified	Early seizures 8% Status epilepticus 2% (OR 2.4) Early seizures no predictor of 30-day case fatality	NS	Very low	NA
Dennis et al. [14]	RS	233 patients	Prophylactic PHT If NCSE diagnosed or if seizures manifested or persisted, additional PHT	101/233 comatose patients In 26/101 performed cEEG monitoring NCSE in 8% of all SAH patients and 31% of patients undergoing to cEEG monitoring Risk factors for NCSE: poor grade, older age, ventriculostomy, cerebral edema ($P < 0.01$)	NS	Low	NA

Table 1 continued

Authors and year	Methods	Population	Treatment assignment	Findings	Aneurysm treatment	Quality of evidence	Balance of benefit vs. harm
Claassen et al. [15]	RS	247	PHT	New-onset epilepsy 7% 4% only one seizure after discharge Predictor of epilepsy: subdural hematoma (OR 9.9, 95% CI 1.9–52.8), cerebral infarction (OR 3.9, 95% CI 1.4–11.3) At 12 months, epilepsy independently associated with severe disability (mRS > 3) (OR 10.3, 95% CI 1.1–22.2) Epilepsy no associated with cognitive impairment	NS	Very low	NA
Byrne et al. [16]	RS	243	Not specified	OS 11% Correlation with MCA location ($P < 0.05$), LOC ($P < 0.01$), AED prescription ($P < 0.001$) LS in 3% of patients (in 1.4%, preexisting epilepsy) LS correlated with previous seizures ($P < 0.05$), CSF shunt ($P < 0.05$), use of AEDs ($P < 0.01$)	Coiling	Very low	NA
Lin et al. [17]	RS	217	PHT	Overall seizure rate: 21.2% OS 7.8% Preoperative seizures 2.3% Postoperative seizures 1.8% Late epilepsy 6.9% Young age (OR 6.6, $P = 0.001$), Fisher greater than 2 (OR 4.3, $P = 0.008$), LOC for more than 1 h (OR 4.3, $P = 0.008$) significantly related to onset seizures OS predictor of persistent neurological deficits (OR 4.2, $P = 0.006$) Factors predicting late epilepsy: LOC more than 1 h (OR 3.6, $P = 0.026$), persistent postoperative neurological deficits (OR 7.1, $P = 0.001$)	Clipping	Very low	NA
Molyneux et al. [18]	Prospective, randomized, controlled clinical trial	2,143	Not specified	Seizures after hospitalization 0.65% Seizures incidence after treatment and before discharge 2.28%: Clipping group 3% Coiling group 1.4% During first year after discharge: Clipping group 2.2 Coiling group 1.3	Coiling ($n = 1,073$) Clipping ($n = 1,070$)	High	NA

Table 1 continued

Authors and year	Methods	Population	Treatment assignment	Findings	Aneurysm treatment	Quality of evidence	Balance of benefit vs. harm
Naidech et al. [19]	Retrospective analysis of a prospectively collected database of adult patients with SAH	527	Exposure to PHT. No active assignment	5% of patients had seizures during hospitalization 13% of patients exposed to PHT > 14 days PHT burden associated with poor functional outcome at 14 days (OR 1.5, $P < 0.001$) In-hospital seizures associated with functional disability in univariate model (OR 4.1, $P = 0.002$)	Clipping 344 (65%), Coiling 83 (16%) No repair 100 (19%)	Very low	Uncertain trade-off
Claassen et al. [20]	Observational	756 patients cEEG monitoring and 3-month mRS available in 116 patients	PHT	Presence of PED independently associated with poor outcome (OR 9, $P = 0.011$)	Clipping in 62% of cases	Low	NA
Claassen et al. [2]	RS	29,998	Not specified	GCSE in 0.2% of patients GCSE independently associated with higher hospital mortality (48% vs. 33%, $P = 0.002$) and longer hospital stay (9 vs. 7 days, $P = 0.016$)	Clipping and coiling	Low	NA
Little et al. [21]	RS	389	Combination of AEDs (PHT, levetiracetam, phenobarbital; lorazepam and pentobarbital second-line therapy)	NCSE in 3% of patients Old age, female sex, ventriculostomy, poor neurological grade, thick cisternal blood clots, structural lesions, common findings in NCSE ($P < 0.05$)	49% clipping 42% endovascular treatment	Low	NA
Rosengart et al. [22]	Retrospective analysis of prospectively collected data	3,552 patients enrolled into 4 prospective, double-blind, placebo-controlled trials investigating the usefulness of tirilazad in SAH	PHT in 52.8% Phenobarbital in 18.7% Carbamazepine in 2.3%	Intraclass correlation coefficient ($P < 0.001$): Study country 0.22 Study center 0.66 Patient treated with AEDs has OR 1.87 for worse neurological outcome ($P = 0.003$) OR 1.87 for vasospasm ($P = 0.001$) OR 1.61 for neurological deterioration ($P = 0.001$) OR 1.33 for cerebral infarction ($P = 0.04$) OR 1.36 for elevated temperature ($P = 0.03$)	NS	Very low	Uncertain trade-off
Chumnanvej et al. [23]	Retrospective analysis of prospectively collected data	453	PHT	3-day PHT regimen produced significant reduction ($P = 0.002$) in the rate of PHT complications	Clipping	Very low	Uncertain trade-offs
Szaflarski et al. [24]	RS	6,044 strokes: 169 patients with SAH	Not specified	Seizure in SAH in 10.1% within 25 h	NS	Low	NA

Table 1 continued

Authors and year	Methods	Population	Treatment assignment	Findings	Aneurysm treatment	Quality of evidence	Balance of benefit vs. harm
Lin et al. [25]	RS	137	81% of patients treated with PHT	Acute symptomatic seizures in 11.7% Unprovoked seizures in 3.6% Mean GOS 3.5 in patients with seizures, 3.1 in patient without seizures Seizures not significant predictor of prognosis after 1-year follow-up	Coiling in 57 patients Clipping in 80 patients	Low	NA
Choi et al. [26]	RS	547	Valproate in 72.4%, PHT in 17.6%); other AEDs in 10%	Overall seizure rate 15.2% OS in 6.2% Perioperative seizures in 3.1% Late epilepsy in 3.1% Young age (OR 3.5, $P = 0.001$), poor clinical grade (OR 2.7, $P = 0.015$), hydrocephalus (OR 6.6, $P = 0.001$) and rebleeding (OR 9.1, $P = 0.001$) related to onset seizures Initial amount of SAH (OR 1.81, $P = 0{,}038$) and cortical infarction (OR 2.04, $P = 0{,}001$) independent risk factors of late epilepsy AEDs adverse effects in 23.4%	Clipping	Low	NA
Lewis et al. [27]	RS	107	16% patients levetiracetam, 84% patients PHT	Significant differences favoring levetiracetam group at the time of the discharge (GOS 4.59 vs. 3.33, $P < 0.01$)	NS	Low	NA
Shah et al. [28]	RS	176	PHT levetiracetam if adverse event with PHT	Levetiracetam has superior tolerability Adverse events higher in PHT group	NS	Low	NA

AED antiepileptic drug, *CSF* cerebrospinal fluid, *CT* computed tomography, *cEEG* continuous electroencephalography, *GCSE* generalized convulsive status epilepticus, *GOS* Glasgow Outcome Scale, *ICH* intracerebral hemorrhage, *LOC* loss of consciousness, *LS* late seizures, *mRS* modified Rankin Scale, *NA* not applicable, *NCSE* non-convulsive status epilepticus, *NS* not specified, *OR* odds ratio, *OS* onset seizures, *PED* periodic epileptiform discharge, *PHT* phenytoin, *RS* retrospective study, *SAH* subarachnoid hemorrhage, *SC* single center

seizures after the first year remains low. While most authors have reported no statistically significant correlation between onset seizure (seizures occurring at the time of SAH) and late epilepsy [5, 15, 17, 25, 26, 35, 41], one study found onset seizures to be an independent risk factor for delayed (< 6 weeks) seizures [1].

There is a trend toward decreasing incidence of seizures after SAH over time [1, 12, 16, 22, 42]. This decreasing trend probably reflects changes in treatment strategies over time, such as the introduction of endovascular therapy [10, 22].

Non-Convulsive Seizures

Most incidence data for seizures in patients with aneurysmal SAH reflect clinically evident seizures consisting of either focal or generalized tonic/clonic activity. Non-convulsive electrical epileptiform activity may also occur after SAH. Non-convulsive seizures and status are not associated with clinically evident phenomena and have been reported after SAH, particularly in patients with poor neurological condition. Claassen and colleagues performed a retrospective analysis of 29,998 patients, using data from the National Inpatient Sample (NIS) database collected between 1994 and 2002 [2]. This study identified convulsive status epilepticus in about 0.2% of non-traumatic SAH patients [2]. Using continuous electroencephalography (cEEG) monitoring in patients with poor-grade SAH, researchers identified non-convulsive status epilepticus in 8 of 101 SAH patients treated in a neurological intensive care unit with unexplained coma or neurological deterioration [14]. They postulated that routine postoperative cEEG monitoring of patients with SAH who are at high risk for non-convulsive status epilepticus might permit earlier diagnosis and treatment to maximize treatment outcome. Claassen and colleagues subsequently performed a retrospective study of 756 patients with SAH who received cEEG [20]. Outcome was unfavorable in all patients with periodic lateralized epileptiform discharges, absence of sleep architecture, and electrographic status epilepticus, and in 92% of patients with non-convulsive status epilepticus. The authors concluded that the cEEG monitoring can provide prognostic information in poor-grade SAH patients. Despite the lack of evidence that cEEG monitoring improves outcome, clinicians often favor using this in SAH patients with depressed mental status to help diagnose non-convulsive seizures and dictate AED initiation [21, 35, 43, 44].

Anticonvulsants after SAH

AED prophylaxis after SAH is a common clinical practice [26, 27, 45]. No randomized controlled trials have investigated the safety and effectiveness of AEDs in SAH after aneurysmal rupture. Most recommendations on seizure prophylaxis after SAH are extrapolated from studies in patients after head injury or intracerebral hemorrhage, or patients with brain tumors [46–48]. Lack of data in aneurysmal rupture patients results in uncertainty regarding the need for AED prophylaxis, choice of drug, dosing, and duration of treatment. Because of the lack of evidence, use of AEDs in patients with SAH varies widely between institutions and physicians [22]. In an analysis of four randomized trials of tirilazad mesylate in SAH conducted worldwide between 1992 and 1997, 65% of patients received prophylactic AEDs. Those data contrast with results from a survey of 100 German neurosurgical departments about SAH management conducted in 2004 [49]. In that survey, AED prophylaxis was used routinely by only 4% of the physicians surveyed. The current uncertainty regarding the use of AEDs in SAH is reflected in the cautious wording of the most recent update of the guidelines of the American Heart Association published in 2009 that concluded that "the administration of prophylactic anticonvulsants *may be considered* in the immediate posthemorrhagic period (Class IIb, Level of evidence B)" [50]. A Cochrane review with the aim to assess the effects of AEDs for the primary and secondary prevention of seizures after SAH is ongoing [51].

Negative Impact of AEDs on Outcome

Due to lack of data and evidence-based guidelines, AED treatment after SAH is determined predominately by the individual treating physician, with substantial variability among centers and countries worldwide. There is growing evidence to suggest that AEDs, and especially phenytoin, have a deleterious effect on outcome. A relationship between AED treatment after SAH and outcome was evaluated using pooled analysis of 3,552 patients with patients enrolled in the four trilizad trials [22]. In this sample, 65% of patients were treated with at least one AED, 8% with two AEDs, and 0.1% AEDs. Phenytoin was the most frequently prescribed AED (52.8%), followed by phenobarbital (18.7%) and carbamazepine (2.3%). AED usage varied dramatically among countries involved in the study and within the same country among different centers. In this subgroup analysis, 90% of patients underwent surgical clipping. Outcome was defined by the Glasgow Outcome Scale at 3 months, after adjusting for study center, World Federation of Neurosurgeons (WFNS) severity grade, patient age, and blood pressure. An unfavorable outcome was more common in patients treated with AEDs. Other secondary end points, including risk of clinical vasospasm, neurological worsening, cerebral infarction, and elevated temperature at day 8 of

hospitalization, were also significantly more common in patients treated with AEDs. Interpreting data from this study is hampered by design limitations, such as the inability to assess duration of AED treatment or to distinguish between patients treated with prophylactic AEDs and patients administered AEDs after suffering a seizure. Nevertheless, this large analysis of patients prospectively enrolled in randomized studies supports safety concerns with routine use of AEDs in patients with SAH.

Naidech and coworkers also linked phenytoin treatment after SAH with neurological and cognitive recovery in a sample of 527 patients [19]. In this study, phenytoin burden was defined as the average serum phenytoin level multiplied by number of days between the first and last measurements, up to a maximum of 14 days. These authors linked prophylactic phenytoin with poor functional and cognitive outcome in a dose-dependent manner [19].

Most of the studies available on the issue of AEDs and seizures after SAH have analyzed the effects of phenytoin. Thus, the potential risks and benefits of newer generation AEDs are unknown and a potential topic for further studies [28, 35, 52, 53].

Duration of AEDs Treatment

When prophylactic AEDs are used in patients with SAH, evidence suggests that a short course of therapy may be as effective as a longer course. In 453 patients with spontaneous SAH managed homogeneously at a single center, a comparison was made between a routine 7-day prophylaxis and a shorter 3-day course [23]. The authors reported a significant reduction in phenytoin-associated complications ($P = 0.002$) without a difference in the rate of seizures using the shorter duration treatment [23]. In patients suffering a seizure during hospitalization, the literature describes continuation of AED therapy for a variable period (6 weeks to 6 months) [5, 11, 16, 19, 22, 23, 26, 33, 54, 55], although there are no strong data to support a particular treatment duration.

Conclusions

Seizures and seizure-like phenomena are not uncommon at the onset of SAH. In patients with an unsecured aneurysm, a seizure is often the expression of rebleeding. Patients at higher risk for developing seizures after SAH are patients with intraparenchymal hematomas, cerebral infarct, middle cerebral artery location, and hydrocephalus [49, 56, 57]. Patients with onset seizure do not appear to be at higher risk for subsequent seizures. Non-convulsive seizures should also be considered in SAH patients with unexplained coma or neurological deterioration. Patients undergoing endovascular embolization have a low risk of peri-procedural seizures [16, 18, 31]. AED prophylaxis remains controversial; however, phenytoin prophylaxis appears to be associated with worse outcome, especially when treatment is more prolonged.

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