

Seizure Prophylaxis in the Immediate Post-Hemorrhagic Period in Patients with Aneurysmal Subarachnoid Hemorrhage

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Abstract

Introduction—Seizures are a well-known complication of aneurysmal subarachnoid hemorrhage (aSAH) and occur most commonly in the immediate posthemorrhagic period. Most commonly used antiepileptic drugs (AEDs) for seizure prophylaxis in aSAH include phenytoin and levetiracetam. There is no reliable data available on the safety and efficacy of restricting AED prophylaxis only till the aneurysm is secured.

Methods—We retrospectively chart reviewed patients admitted to our neurosciences intensive care unit (NICU) with aSAH during the past two years. Seizure incidence was studied in patients treated with phenytoin versus levetiracetam and in patients treated for 3–7 days vs. those where AED was discontinued immediately after aneurysm was secured.

Results—In 28 patients, AED prophylaxis was discontinued immediately after the aneurysm was secured, and in 21 patients, it was continued for 3–7 days. Of the 28 patients who received AED prophylaxis for less than or equal to two days, phenytoin was used in 20 patients and levetiracetam was used in eight patients. In patients receiving AED prophylaxis for 3–7 days, phenytoin was used in eight cases and levetiracetam was used in 13 cases. None of these patients had seizures reported during hospitalization or at three-month follow-up.

Conclusion—Stopping the AED prophylaxis immediately after aneurysm coiling is not associated with increased risk of seizures. Seizures at presentation in patients with aSAH are not associated with development of epilepsy at three months. Both phenytoin and levetiracetam are well tolerated in patients with aSAH when limited to the immediate posthemorrhagic period.

Keywords

aneurysmal subarachnoid hemorrhage; seizures; antiepileptic drugs; phenytoin; levetiracetam

Introduction

Seizures have been reported in up to 6–26% of patients after aneurysmal SAH (aSAH) [1–7]. Variation in incidence of post-aSAH seizures is likely the result of patient selection methods (such as site of aneurysm, surgical clipping vs. endovascular coiling), timing of post-SAHA seizures, and the administration of prophylactic antiepileptic drugs (AEDs) after admission to the intensive care unit (ICU) [7]. Simple partial seizures with or without secondary generalization are the most commonly reported seizure type in this patient population, with nonconvulsive status epilepticus being reported in

~18% of patients following aSAH [1,7–9]. After three decades of research, the indication and duration of AED use following aSAH is still controversial. Also, the reported side effects of AEDs and associated in-hospital complications (especially, phenytoin, the most commonly used AED in Neurosciences ICU (NICU) in aSAH patients make the decision to start seizure prophylaxis more challenging in such patients. We retrospectively studied the incidence of early (< seven days) and late (< three months) onset seizures following aSAH and compared the duration of seizure prophylaxis, i.e., stop-

Table 1. Patient characteristics

Patient characteristics	Number of patients (percentage)
Anterior circulation aSAH	40 (82%)
Posterior circulation aSAH	9 (18%)
Seizures at presentation	7 (14%)
Glasgow comma scale < 13 at presentation	9 (18%)
Modified FS \geq 3 at presentation	29 (59%)
Hunt & Hess score \geq 3 at presentation	18 (37%)
Vasospasm during hospitalization	1 (2%)
Other significant complications related to AED use	0
mRS \leq 2 at three-month follow-up	46 (94%)
mRS $>$ 2 at three-month follow-up	3 (6%)

ping AED prophylaxis after the aneurysm was secured versus 3–7 days of seizure prophylaxis, as recommended in the Neurocritical Care Society (NCS) guidelines [10]. We also calculated the incidence of in-hospital and late onset complications related to AED prophylaxis in patients receiving phenytoin versus levetiracetam.

Methods

We retrospectively reviewed patients admitted to our NICU with aneurysmal subarachnoid hemorrhage (aSAH) during the academic year July 2014 to June 2016. A total of 49 patients were admitted during this time period with diagnosis of aSAH who underwent endovascular coil embolization and were treated with AEDs. Choice of AED was at the discretion of the attending neurointensivist. Phenytoin was initiated with a 15–20-mg/kg load followed by 100-mg TID maintenance, adjusting this as needed based on levels, and levetiracetam was mostly initiated with a loading dose of 1000–1500 mg followed by 500–1000-mg BID maintenance dosage.

Seizure characteristics were retrospectively studied from hospital admission records and office visits. Demographic variables (sex, age, smoking history, and medical co-morbidity), radiologic information (Glasgow coma Scale score, Hunt and Hess grade, and modified Fisher grade), location of aneurysm, clipping versus coiling, evidence of vasospasm, delayed ischemic neurologic deficits (DIND), length of hospital stay, seizures (at presentation, discharge, and three-month office visit), and modified Rankin Scale (mRS) at three months were collected. Seizures observed in the prehospital setting by family members or caregivers, paramedics, and ED staff were also recorded. Patients with suspicion for nonconvulsive seizures were monitored using continuous EEG.

The seizure incidence was documented according to onset from ictus, i.e., seizure onset:

1. prior to endovascular coil embolization,
2. within seven days of ictus, and
3. seven days to three months postictus.

Patients were followed up at three months in the clinic. mRS was used to assess functional outcome at follow-up, based on clinic progress notes, as well as assessments from the rehabilitation team including occupational, speech, and physical therapists.

Patients in whom AED prophylaxis was continued for more than seven days, patients with nonaneurysmal SAH, those who died within 72 hours, and patients with a pre-existing seizure disorder were excluded from the study.

Results

In 28 patients who underwent endovascular coil embolization, AED prophylaxis was discontinued immediately after the aneurysm was secured (which was less than or equal to two days from aneurysm rupture in all the cases) and was continued for 3–7 days in 21 patients (Table 1). Of the patients who received AED prophylaxis for less than or equal to two days, 22 patients had aSAH from aneurysmal rupture in anterior circulation, while 6 had posterior circulation aSAH. Of the patients who received AED prophylaxis for 3–7 days, 17 had anterior circulation, while 4 had posterior circulation aSAH.

In total, 29 patients had a modified Fischer score (mFS) greater than or equal to 3, and 18 patients had a Hunt & Hess (H&H) score of greater than or equal to 3. Of the 28 patients who received AED prophylaxis for less than or equal to two days, phenytoin was used in 20 patients and levetiracetam was used in 8 patients. In patients who received AED prophylaxis for 3–7 days, phenytoin was used in 8 cases and levetiracetam was used in 13 cases. Seven (14%) of all these patients had at least one clinical seizure in the field or in the emergency room prior to administration of an AED but none had seizures reported during hospitalization or at a three-month follow-up. Of these patients, 46 had mRS less than or equal to 2 at their three-month follow-up. Only one patient had radiographic vasospasm detected on routine computed-tomography angiogram of the head but none had any evidence of DIND. One patient died during hospitaliza-

Table 2. Duration of AED prophylaxis and incidence of seizures in each group

AED	Number of patients where AED was discontinued immediately securing the aneurysm (percentage)	Number of patients where AED was used for 3–7 days (percentage)	Seizures at discharge	Seizures on three months follow-up
Keppra	8 (16%)	13 (26%)	0	0
Phenytoin	20 (41%)	8 (16%)	0	0
Total number of patients	28 (57%)	21 (43%)	0	0

tion which was predicted by poor H&H and mFS at presentation. The pertinent patient characteristics are summarized in Table 2.

Discussion

The purpose of this study is to report our experience with early and late-onset seizures, in-hospital complications (including DIND) and functional outcome at three months in patients with aSAH who were treated with AEDs. We also compared patients treated with phenytoin versus levetiracetam and patients treated for 3–7 days versus those in whom AEDs were discontinued immediately after the aneurysm was secured.

Seizures are a well-known complication of aSAH, with an incidence of 6–26% [1,3,4,11] and occur most commonly in the immediate posthemorrhagic period [12,13]. Risk factors include younger age, middle cerebral artery aneurysms, higher Fisher and Hunt & Hess scales at presentation, associated intraparenchymal hemorrhage, and patients undergoing surgical clipping of aneurysms [2,4,7]. Seizures following aSAH can have both immediate complications (e.g., increased risk of rebleeding, increased intracranial pressures, and metabolic stress) and late complications (e.g., epilepsy, poor outcome on days 30 to 90 from aneurysm rupture) [6,10,11,14]. AEDs have been used in patients following aSAH to prevent immediate seizures and reduce the risk of development of epilepsy. Although many studies have been published regarding the use of AEDs in aSAH, there is no enough data to strongly recommend its routine use as well as the optimum duration of use for seizure prophylaxis.

A number of retrospective studies have shown that there is no significant difference between groups with or without seizure prophylaxis in terms of seizure outcome and that there is increased risk of worse outcomes (such as vasospasm, cerebral ischemia, drug-induced fever, and compromised cerebral perfusion pressures) secondary to AED use in such patients [14–17]. On the other hand, studies have also demonstrated increased risk of late seizures in patient not on AED prophylaxis compared with those who were treated with AEDs early [2,6,11,12,18–20].

Most commonly used AEDs for seizure prophylaxis in patients with aSAH include phenytoin and levetiracetam. Phenytoin has been associated with increased risk of DIND, drug-induced fever, and mild cognitive dysfunction at three months [6,10]. Both NCS and the American Heart Association (AHA) guidelines encourage the use of AEDs in the immediate posthemorrhagic period (3–7 days from ictus), but routine long-term use of AEDs is not recommended by either guidelines in patients with aSAH. NCS guidelines recommend against the use of phenytoin for seizure prophylaxis in patients with aSAH [10], while the AHA recommends the use of AEDs in such patients without specifying the drug of choice [21]. Importantly, no reliable data or guidelines are available regarding the safety and efficacy of stopping AED prophylaxis once the aneurysm is secured.

After retrospectively reviewing patients admitted to our NICU with aSAH over the past two years, we did not find any significant difference between patients whose AEDs were stopped once the aneurysm was secured, compared with those who received prophylaxis for 3–7 days per NCS and AHA guidelines. No difference was noted between phenytoin and levetiracetam usage. Also, the choice of AEDs did not cause any of the complications previously reported with AED use in aSAH patients, including cerebral ischemia, drug-induced fever, compromised cerebral perfusion pressures, or hemodynamic instabilities. Most (94%) of our patients were found to have a good functional outcome at three-month follow-up (mRS ≤ 2). Patients, who had seizures at presentation and were treated with AEDs, did not report any further seizures at three months, which further confirms the hypothesis that seizures at presentation in patients with aSAH may be secondary to abnormal posturing or sudden increases in intracranial pressure rather than true epileptic events [1,2,19].

This study has some limitations. It only includes patients who underwent endovascular coil embolization, and hence, our findings may not apply to patients undergoing neurosurgical clipping of the aneurysms. Other limitations to our study include a smaller sample size and retrospective nature of the study. Larger and randomized trials comparing commonly used AEDs with placebo are recommended to justify the routine use of AEDs and

also duration of use for primary and secondary prevention of seizures after aSAH.

Conclusion

AED use in the immediate posthemorrhagic period in patients with aSAH decreases the risk of seizures during hospitalization and at three months from discharge. Stopping AED prophylaxis immediately after the aneurysm is secured and is not associated with increased risk of seizures or other worse outcomes. Seizures at presentation in patients with aSAH are not associated with development of epilepsy at three months. Both phenytoin and levetiracetam are well tolerated in patients with aSAH when limited to the immediate posthemorrhagic period.

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