Clinical Study

Incidence of delayed seizures, delayed cerebral ischemia and poor outcome with the use of levetiracetam versus phenytoin after aneurysmal subarachnoid hemorrhage

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Abstract
Current guidelines recommend against the use of phenytoin following aneurysmal subarachnoid hemorrhage (aSAH) but consider other anticonvulsants, such as levetiracetam, acceptable. Our objective was to evaluate the risk of poor functional outcomes, delayed cerebral ischemia (DCI) and delayed seizures in aSAH patients treated with levetiracetam versus phenytoin. Medical records of patients with aSAH admitted between 2005–2012 receiving anticonvulsant prophylaxis with phenytoin or levetiracetam for >72 hours were reviewed. The primary outcome measure was poor functional outcome, defined as modified Rankin Scale (mRS) score >3 at first recorded follow-up. Secondary outcomes measures included DCI and the incidence of delayed seizures. The association between the use of levetiracetam and phenytoin and the outcomes of interest was studied using logistic regression. Medical records of 564 aSAH patients were reviewed and 259 included in the analysis after application of inclusion/exclusion criteria. Phenytoin was used exclusively in 43 (17%), levetiracetam exclusively in 132 (51%) while 84 (32%) patients were switched from phenytoin to levetiracetam. Six (2%) patients had delayed seizures, 94 (36%) developed DCI and 63 (24%) had mRS score >3 at follow-up. On multivariate analysis, only modified Fisher grade and seizure before anticonvulsant administration were associated with DCI while age, Hunt-Hess grade and presence of intraparenchymal hematoma were associated with mRS score >3. Choice of anticonvulsant was not associated with any of the outcomes of interest. There was no difference in the rate of delayed seizures, DCI or poor functional outcome in patients receiving phenytoin versus levetiracetam after aSAH. The high rate of crossover from phenytoin suggests that levetiracetam may be better tolerated.

1. Background

Anticonvulsant prophylaxis is widely used following aneurysmal subarachnoid hemorrhage (aSAH). Retrospective studies report the rate of seizures after aSAH to be between 1–18% [1–6]. The incidence of delayed or in-hospital seizures may be even lower, 4–8%, when anticonvulsant prophylaxis is used [4–6]. It is not known whether the choice of anticonvulsant used for prophylaxis has an impact on the subsequent risk of seizures or poor outcomes after aSAH. A retrospective study of patients with aSAH found that phenytoin burden may be associated with poor cognitive outcome at 3 months [7]. Current guidelines from the Neurocritical Care Society (NCS) therefore specifically recommend against the routine use of phenytoin for prophylaxis [2], while the American Heart Association guidelines state that the use of anticonvulsants is reasonable, without specifically recommending against or for any particular anticonvulsant [1]. Unlike the case with phenytoin, the NCS guidelines do not specifically recommend against the use of other anticonvulsants, and state that alternate anticonvulsants may be considered for prophylaxis for a duration of 3–7 days from ictus [2,3]. While levetiracetam is a popular alternative to phenytoin, the relative value of alternate anticonvulsants such as levetiracetam has not been systematically addressed, and it is not clear that their routine use is associated with better outcomes compared to the use of phenytoin in this specific setting. One study suggests that the short term use of levetiracetam may be...
associated with an increase in the rate of late seizures compared to a longer duration of prophylaxis with phenytoin [8]. To our knowledge the specific risk of delayed cerebral ischemia (DCI) with levetiracetam versus that with phenytoin has also not been systematically evaluated – a relevant question in view of the association between phenytoin burden, fever and poor outcomes [7,9,10]. It is also possible that a less efficacious anticonvulsant may increase the risk of DCI through the mechanism of delayed seizures and increased metabolic demand, as has been previously described [11]. One animal study has demonstrated a decreased risk of poor neurological outcomes as well as vasospasm associated with the use of levetiracetam after aSAH [12]. To our knowledge there is no study in the literature directly comparing the risk of delayed seizures, DCI and poor outcomes associated with the use of levetiracetam versus phenytoin in patients with aSAH.

We aimed to compare the rate of poor functional outcomes, delayed seizures and DCI in patients treated with phenytoin versus levetiracetam following aSAH.

2. Methods

Approval for this study was obtained from the University of Michigan’s Institutional Review Board (HUM00050017). The medical records of patients with an aSAH admitted between January 2005 and February 2012 were reviewed. Patients with aSAH receiving phenytoin or levetiracetam for at least 72 hours following admission were included. Patients with non-aneurysmal etiology, age <18 years, non-availability of CT scan within 24 hours of onset, modified Fisher grade 0–1, those who died within 72 hours and patients with a pre-existing seizure disorder were excluded.

2.1. Outcomes of interest

The primary outcome of interest was poor functional outcome at first recorded follow-up. Follow-up was assessed between 6 weeks and 6 months from discharge or at date of last contact following discharge. The modified Rankin Scale (mRS) [13] score was used to assess functional outcome at follow-up, based on specific documentation at the time of Rehabilitation, Neurosurgery and Neurology clinic visits. Poor neurological outcome was defined as mRS score >3. The secondary outcomes of interest were the incidence of seizures following initiation of anticonvulsant prophylaxis (delayed seizures) and the occurrence of DCI. Both clinically apparent as well as non-convulsive seizures detected only on electroencephalography (EEG) were included when determining the incidence of delayed seizures. Continuous EEG monitoring (cEEG) was not routinely performed, however, and was requested only at the discretion of the treating physician. DCI was defined as the composite of symptomatic vasospasm and/or delayed infarction on imaging [14]. Symptomatic vasospasm was defined as a change in neurological status during days 3–14 consisting of neurological worsening lasting ≥2 hours. Neurological worsening was defined as modified Glasgow Coma Scale score decline by 2 or more points, an increase by 2 or more points on the abbreviated National Institutes of Health Stroke Scale, or a new focal neurological deficit or new hypodensity on head CT scan with clinical signs. Symptoms must not have been explained by hydrocephalus, surgical trauma, new hemorrhage, recognized seizure, fever, sedation, hypoxia, infection, or metabolic abnormality, and must have been thought to be due to symptomatic vasospasm by the treating team, including the attending neurointensivist and neurosurgeon. Delayed infarction was documented on head CT scan between day 3 and 6 weeks from ictus and could not be procedure related.

2.2. Variables of interest

The primary variables of interest were the use of phenytoin or levetiracetam for at least 72 hours within the first week after aSAH. Seventy-two hours was considered the threshold for “significant” use of phenytoin and other anticonvulsants since some authors as well as the current guidelines from the NCS recommend that anticonvulsant use following aSAH be confined to a 3–7 day period [2,15]. All changes from one anticonvulsant to another were recorded, along with the reason for the change if documented in the medical record.

All seizures that occurred in the risk period for delayed cerebral ischemia (up to 21 days from admission), including those observed in the pre-hospital setting and emergency room prior to anticonvulsant initiation, as well any seizures occurring following initiation of anticonvulsant therapy (delayed seizures), were recorded and analyzed as variables in association with the outcomes of DCI and poor functional outcome. We analyzed the occurrence of seizures in these two different clinical settings (i.e., seizures occurring pre and post-initiation of anticonvulsant) as separate variables in association with the outcomes of interest since the pathophysiology, prognostic significance and implications for treatment are potentially very different for seizures occurring at the time of ictus versus those occurring at a later time despite the use of anticonvulsant prophylaxis. Other variables analyzed for association with delayed cerebral ischemia and poor functional outcome were age, race, sex, smoking history, history of hypertension, Hunt and Hess grade [16], modified Fisher grade [17], presence of intracerebral hematoma, aneurysm location, aneurysm size and the use of clipping versus coiling.

2.3. Management protocol

Every effort was made to secure the aneurysm with microsurgical clipping or endovascular coiling within 24 hours of admission. All patients were admitted to the neuro-intensive care unit for monitoring. External ventricular drainage was performed for hydrocephalus. Anticonvulsants were started on admission for all patients, continued for the duration of the inpatient admission and tapered off within 30 days following discharge, unless the patient had suffered a seizure and required ongoing anticonvulsant use. Choice of anticonvulsant was at the discretion of the attending neurosurgeon or neurointensivist. Phenytoin was typically initiated with a 20 mg/kg intravenous load and then continued at a dose of 4–6 mg/kg/day. Phenytoin levels were not routinely measured on a daily basis and were ordered intermittently at the discretion of the treating physician. Aggressive supplementation to maintain “therapeutic” levels was not routinely performed and the phenytoin burden could not therefore be reliably estimated. Levetiracetam was typically initiated at 250–500 mg twice daily and further dose adjustments were at the discretion of the treating physician. cEEG monitoring was ordered at the discretion of the treating physician. Nimodipine was used in all patients for 21 days if hemodynamically tolerated. A magnesium infusion (fixed dose of 0.5 g/hour) was used in all patients for 14 days. The infusion was not titrated to target levels and serum levels were measured inconsistently. The goal of fluid management was euvoemia using normal saline in all patients. Patients with otherwise unexplained acute neurological deterioration were given a bolus of crystalloid or colloid and had their blood pressure augmented by 20–30% using vasopressors. Augmentation of cardiac index was variably performed. Angiographic imaging with either digital subtraction angiography or CT angiography was performed as soon as possible in all patients with neurological deterioration following a non-contrast head CT scan, regardless of response to hemodynamic augmentation.
2.4. Statistical analysis

The D’Agostino–Pearson test was used to determine if variables demonstrated normal distribution. Mean and standard deviation (SD) with range was calculated for continuous variables with normal distribution. For variables without normal distribution, the median with interquartile range was used. To test whether there was a bivariate association between categorical variables and the outcomes of interest, chi-squared or Fisher’s exact test was used. Bivariate associations of continuous patient variables with a normal distribution were assessed with the independent sample two-tailed Student’s t-test and continuous variables with non-normal distributions were assessed with the Mann–Whitney U test. Multivariate logistic regression models to identify independent associations among variables of interest and the outcomes of interest were built. With our explanatory variables of interest (exposure to phenytoin and levetiracetam) and occurrence of seizures before and after anticonvulsant use forced into the models, additional covariates were chosen based on an association with DCI or functional outcome using a liberal threshold of approximately p < 0.2 on unadjusted bivariate analysis. In addition to the multivariate analysis to examine the association of exposure to phenytoin and levetiracetam for ≥72 hours with the outcomes of interest, we also performed a predetermined multivariate analysis of the association between the choice of anticonvulsant (phenytoin OR levetiracetam, as a single variable) and outcomes of interest in the subgroup of patients treated with a single anticonvulsant for the entire course of their admission, to exclude the confounding effect of crossover from one anticonvulsant to another. Statistical analyses were performed using MedCalc version 12.7.5.0 (MedCalc software, Mariakerke, Belgium).

3. Results

The medical records of 564 patients with subarachnoid hemorrhage were reviewed. Of these, 559 received at least 72 hours of either phenytoin or levetiracetam in the first week after aSAH. One hundred fifty-one were excluded based on non-aneurysmal etiology, 98 based on the absence of initial CT scan and/or death within 72 hours of admission, and 51 for modified Fisher grade 0–1 on initial CT scan. Two hundred fifty-nine patients with aSAH met criteria and were included in the analysis. The mean age was 55 years (SD 13 years, range 23–90). There were 192 (74%) women and 67 (26%) men.

3.1. Anticonvulsant use

Of the 259 patients who were studied, 127 (49%) received phenytoin for at least 72 hours following admission while levetiracetam was used for ≥72 hours following admission in 132 (51%). Of the 127 patients initially treated with phenytoin, 84 (66%) were subsequently changed over to levetiracetam. No patient was changed from levetiracetam to phenytoin. Of the 84 patients who were switched from phenytoin to levetiracetam during their hospital stay, 30 had a reason for the change documented in medical records. Twelve were documented as having been changed for fever alone, 10 were changed because of difficulty maintaining therapeutic serum levels of phenytoin, five for the appearance of a new rash, two for both fever and a new rash, and one in an attempt to optimize cognitive recovery.

3.2. Seizures

Twenty-seven of 259 patients (10%) had seizures at any time after aneurysm rupture. Twenty-one (8% of all patients) had at least one clinical seizure in the field or in the emergency room prior to administration of an anticonvulsant. Of these patients, 12 were loaded with phenytoin on arrival to the hospital while nine were treated with levetiracetam. Six of 259 (2%) patients had a seizure following initiation of anticonvulsant prophylaxis (delayed seizures). All were overt clinical seizures, there were no isolated electrographic/non-convulsive seizures documented in our series. Three patients were on phenytoin at the time of their seizure, occurring 2, 7 and 10 days after admission. One patient had a seizure 11 days after admission, 6 days after being switched to levetiracetam from phenytoin. Two other patients had seizures while on levetiracetam, at 2 and 10 days following admission. All pre-anticonvulsant seizures were recorded as being generalized tonic-clonic. The clinical manifestation of all delayed seizures included a transient decrease in the level of alertness with varied motor manifestations. Motor manifestations were generalized tonic-clonic (one patient), posturing (three patients), eye deviation (one patient), eye deviation plus arm jerking (one patient) and rhythmic facial twitching (one patient). No patient had both a pre-anticonvulsant seizure as well as seizure after starting anticonvulsant.

### Table 1

| Variable                        | Delayed cerebral ischemia absent n = 165 | Delayed cerebral ischemia present n = 94 | p value |
|---------------------------------|-----------------------------------------|------------------------------------------|---------|
| Age, years, mean ± SD           | 56 ± 14                                  | 55 ± 12                                  | 0.94    |
| Female sex                      | 121 (73%)                                | 71 (76%)                                 | 0.81    |
| Race                            | 5                                        | 1                                        | 0.66    |
| Asian                           | 13                                       | 8                                        |         |
| Black                           | 136                                      | 81                                       |         |
| Caucasian                       | 2                                        | 0                                        |         |
| Hispanic                        | 9                                        | 4                                        |         |
| Smoker                          | 81 (50%)                                 | 47 (50%)                                 | 0.99    |
| Hypertension history            | 72 (44%)                                 | 49 (52%)                                 | 0.25    |
| Hunt and Hess grade             |                                          |                                          | 0.0001* |
| 1                               | 29 (18%)                                 | 7 (7%)                                   |         |
| 2                               | 57 (35%)                                 | 19 (20%)                                 |         |
| 3                               | 45 (26%)                                 | 32 (34%)                                 |         |
| 4                               | 18 (11%)                                 | 30 (32%)                                 |         |
| 5                               | 16 (10%)                                 | 6 (6%)                                   |         |
| Modified Fisher grade           |                                          |                                          | <0.0001*|
| 2                               | 19 (11%)                                 | 3 (3%)                                   |         |
| 3                               | 120 (73%)                                | 50 (53%)                                 |         |
| 4                               | 26 (16%)                                 | 41 (44%)                                 |         |
| Intracerebral hematoma          | 34 (21%)                                 | 31 (33%)                                 | 0.04*   |
| Aneurysm artery location        | 47                                       | 37                                       | 0.38    |
| Anterior communicating          |                                          |                                          |         |
| Posterior communicating         |                                          |                                          |         |
| Middle cerebral                 | 40                                       | 25                                       |         |
| Posterior inferior cerebellar   | 26                                       | 11                                       |         |
| Internal carotid                | 11                                       | 6                                        |         |
| Basilar                         | 13                                       | 4                                        |         |
| Other                           |                                          |                                          |         |
| Aneurysm size, median           | 6 mm (4–8)                               | 6 mm (4–9)                               | 0.95    |
| (interquartile range)           |                                          |                                          |         |
| Microsurgical clipping performed| 83 (50%)                                 | 49 (52%)                                 | 0.09*   |
| Phenytoin use ≥72 hours          | 83 (50%)                                 | 44 (47%)                                 | 0.68*   |
| Levetiracetam use               | 135 (81%)                                | 81 (86%)                                 | 0.46*   |
| ≥72 hours                       |                                          |                                          |         |
| Seizure before anticonvulsant   | 8 (5%)                                   | 13 (14%)                                 | 0.02*   |
| Seizure after anticonvulsant    | 4 (2%)                                   | 2 (2%)                                   | 1.00*   |

Data are presented as n (%) unless otherwise stated.

SD = standard deviation.

* Included in multivariate analysis.
There was no statistically significant association between exposure to phenytoin \( \geq 72 \) hours \( (p = 0.44) \) and occurrence of delayed seizures. There was a trend toward fewer seizures in patients exposed to levetiracetam \( \geq 72 \) hours \( (p = 0.06) \), with 3/216 (1%) patients exposed to levetiracetam versus 3/43 (7%) never exposed to levetiracetam suffering delayed seizures; however, the predetermined threshold for statistical significance \( (p < 0.05) \) was not reached. In the subgroup of patients treated with a single anticonvulsant for the duration of their admission, again there was no statistically significant association between choice of anticonvulsant (phenytoin OR levetiracetam) and occurrence of delayed seizures \( (p = 0.10) \). The number of delayed seizures \( (n = 6) \) was too small to permit meaningful multivariate analysis.

### 3.3. DCI

Overall, 94 of 259 (36%) patients had DCI. Table 1 depicts the distribution of variables in patients with and without DCI. Hunt and Hess grade, modified Fisher grade, presence of intracerebral hematoma, performance of microsurgical clipping and seizure prior to anticonvulsant use attained the \( p < 0.2 \) threshold on bivariate analysis for inclusion in the multivariate model. When these variables, plus use of phenytoin, use of levetiracetam, seizure prior to anticonvulsant use and seizure after anticonvulsant initiation were included in a multivariate logistic regression analysis, only modified Fisher grade 4 (odds ratio [OR] 4.47, 95% confidence interval [CI] 2.18–9.13, \( p < 0.0001 \)) and seizure before anticonvulsant administration \( (OR 6.30, 95\% CI 2.01–19.76, p = 0.002) \) were found to attain statistical significance for association with DCI. In the multivariate analysis of patients treated with only one anticonvulsant through the course of their hospital stay \( (n = 175, Table 2) \), again only modified Fisher grade 4 \( (OR 4.22, 95\% CI 1.70–10.45, p = 0.002) \) and seizure before anticonvulsant administration \( (OR 4.62, 95\% CI 1.13–18.80, p = 0.03) \) were found to attain statistical significance for association with DCI.

The two components of DCI, symptomatic vasospasm \( (n = 81) \) and delayed infarction \( (n = 57) \) were found in 31% (86% of patients with DCI) and 22% (61% of patients with DCI) of all patients, respectively. Forty-four patients (17% of all patients, 47% of patients with DCI) had both symptomatic vasospasm and DCI. The distribution of seizures and anticonvulsant use in patients with and without symptomatic vasospasm and delayed infarction is shown in Table 3. Seizure prior to anticonvulsant use was the only variable to attain statistical significance on bivariate analysis, with most of the association with DCI resulting from a statistically significant association \( (p = 0.01) \) with delayed infarction.

### 3.4. Poor neurological outcome

Of 259 patients, 63 (24%) had mRS score >3 at follow up. Table 4 depicts the distribution of variables in patients with and without mRS score >3. Age, smoking history, history of hypertension, Hunt and Hess grade, modified Fisher grade, presence of intracerebral hematoma and treatment modality (coiling versus microsurgical clipping) attained the \( p < 0.2 \) threshold on bivariate analysis for inclusion in the multivariate analysis, along with the forced inclusion of the variables of interest – use of phenytoin, use of levetiracetam, seizure prior to anticonvulsant use and seizure after anticonvulsant initiation. Following logistic regression age (OR

### Table 2

| Variable | Delayed cerebral ischemia absent | Delayed cerebral ischemia present | \( p \) value |
|----------|---------------------------------|----------------------------------|-------------|
| Age, years, mean ± SD | n = 112 | n = 63 | 0.33 |
| Female sex | 83 (74%) | 47 (75%) | 0.91 |
| Race | | | 0.77 |
| Asian | 3 | 1 | |
| Black | 7 (6%) | 9 (14%) | 0.67 |
| Caucasian | 95 (82%) | 57 (89%) | 0.95 |
| Hispanic | 2 (1%) | 0 (0%) | |
| Other | 5 (4%) | 2 (3%) | |
| Smoker | 51 (46%) | 30 (48%) | 0.91 |
| Hypertension history | n = 175 | 0.0008* |
| 1 | 19 (17%) | 6 (10%) | |
| 2 | 36 (32%) | 12 (19%) | |
| 3 | 31 (28%) | 22 (35%) | |
| 4 | 12 (11%) | 20 (32%) | |
| 5 | 14 (13%) | 3 (5%) | |
| Modified Fisher grade | n = 93 | 0.0008* |
| 2 | 14 (13%) | 2 (3%) | |
| 3 | 80 (71%) | 36 (57%) | |
| 4 | 18 (16%) | 25 (39%) | |
| Intracerebral hematoma | | | 0.33 |
| Aneurysm artery location | | | 0.49 |
| Anterior communicating | 26 | 23 | |
| Posterior communicating | 33 | 19 | |
| Middle cerebral | 14 | 6 | |
| Posterior inferior cerebellar | 8 | 4 | |
| Internal carotid | 12 | 6 | |
| Basilar | 6 | 2 | |
| Other | 13 | 3 | |
| Aneurysm size, median (interquartile range) | 5.65 mm (4–8) | 6 mm (4–8.3) | 0.64 |
| Microsurgical clipping performed | 53 (47%) | 30 (48%) | 0.03* |
| Phenytoin as anticonvulsant | 30 (27%) | 13 (21%) | 0.47* |
| Seizure before anticonvulsant | 7 (6%) | 9 (14%) | 0.13* |
| Seizure after anticonvulsant | 3 (3%) | 2 (3%) | 0.78* |

Data are presented as n (%) unless otherwise stated. SD = standard deviation. * Included in multivariate analysis.

### Table 3

| Variable | Symptomatic vasospasm present | Symptomatic vasospasm absent | \( p \) value |
|----------|-------------------------------|-------------------------------|--------------|
| Phenytoin use \( \geq 72 \) hours | 39 (48%) | 88 (49%) | 0.95 |
| Levetiracetam use \( \geq 72 \) hours | 70 (86%) | 146 (82%) | 0.48 |
| Seizure before anticonvulsant | 10 (12%) | 11 (6%) | 0.15 |
| Seizure after anticonvulsant | 1 (1%) | 5 (3%) | 0.67 |

Data are presented as n (%).

### Table 4

| Variable | Delayed infarct present | Delayed infarct absent | \( p \) value |
|----------|-------------------------|------------------------|--------------|
| Phenytoin use | 26 (46%) | 101 (50%) | 0.66 |
| Levetiracetam use | 47 (82%) | 169 (84%) | 0.99 |
| Seizure before anticonvulsant | 10 (18%) | 11 (5%) | 0.01 |
| Seizure after anticonvulsant | 2 (4%) | 4 (2%) | 0.62 |

Data are presented as n (%).
1.09, 95% CI 1.04–1.13, p < 0.0001), Hunt-Hess grade 1 (OR 0.02, 95% CI 0.001–0.35, p = 0.008), Hunt and Hess grade 5 (OR 23.60, 95% CI 4.76–117.02, p = 0.0001) and presence of intraparenchymal hematoma (OR 3.86, 95% CI 1.56–9.59, p = 0.004) were associated with poor functional outcome. In the multivariate analysis of patients treated with only one anticonvulsant through the course of their hospital stay (n = 175, Table 5), only age (OR 1.11, 95% CI 1.05–1.18, p = 0.0002) and presence of intraparenchymal hematoma (OR 14.96, 95% CI 3.60–62.16, p = 0.0002) attained statistical significance for association with mRS score >3.

4. Discussion

Our study, which to our knowledge is the first to directly compare outcomes related to levetiracetam versus phenytoin use in the setting of aSAH, found no significant difference in the rates of delayed seizures, DCI and poor functional outcome. While a randomized controlled trial of phenytoin versus levetiracetam in a mixed group of patients, 89% of whom had severe traumatic brain injury, found improved neurological and functional outcomes in patients treated with levetiracetam with no difference in the seizure rate, no similar clinical trial has been conducted in the specific setting of aSAH [18]. In our study, delayed seizures were rare when anticonvulsant prophylaxis was used with either levetiracetam or phenytoin. Only six of 259 (2%) patients had a seizure following initiation of an anticonvulsant, consistent with the low rate of delayed seizures reported in other studies [4–6]. This suggests that efficacy – at least when measured by the incidence of overt (as against non-convulsive) seizures – may not be a major consideration in the selection of an agent for anticonvulsant prophylaxis. In addition, the choice of anticonvulsant did not influence the risk of DCI in our study. Only modified Fisher grade and seizure

### Table 4

| Variable                        | Good functional outcome (n = 196) | Poor functional outcome (n = 63) | p value |
|---------------------------------|----------------------------------|---------------------------------|---------|
| Age, years, mean ± SD           | 53 ± 12                          | 63 ± 14                         | <0.0001 |
| Female sex                      | 143 (73%)                        | 49 (78%)                        | 0.55    |
| Race                            | 5                                | 1                               | 0.03    |
| Asian                           |                                  |                                 |         |
| Black                           | 16                               | 5                               |         |
| Caucasian                       | 163                              | 54                              |         |
| Hispanic                        | 2                                | 0                               |         |
| Other                           | 10                               | 3                               |         |
| Smoker                          | 104 (63%)                        | 24 (38%)                        | 0.05    |
| Hypertension history            | 85 (52%)                         | 36 (57%)                        | 0.08    |
| Hunt and Hess grade             |                                  |                                 |         |
| 1                               | 35 (18%)                         | 1 (25%)                         |         |
| 2                               | 70 (42%)                         | 6 (10%)                         |         |
| 3                               | 58 (35%)                         | 19 (31%)                        |         |
| 4                               | 30 (18%)                         | 18 (29%)                        |         |
| 5                               | 3 (2%)                           | 19 (31%)                        |         |
| Modified Fisher grade           |                                  |                                 | 0.04    |
| 2                               | 17 (9%)                          | 5 (8%)                          |         |
| 3                               | 136 (69%)                        | 34 (54%)                        |         |
| 4                               | 43 (22%)                         | 24 (38%)                        |         |
| Intracerebral hematoma          | 33 (20%)                         | 32 (51%)                        | <0.0001 |
| Aneurysm artery location        |                                  |                                 | 0.44    |
| Anterior communicating          | 68                               | 16                              |         |
| Posterior communicating         | 44                               | 21                              |         |
| Middle cerebral                 | 29                               | 8                               |         |
| Posterior inferior cerebellar   | 12                               | 5                               |         |
| Internal carotid                | 17                               | 6                               |         |
| Basilar                         | 15                               | 2                               |         |
| Other                           | 11                               | 5                               |         |
| Aneurysm size, median (interquartile range) | 6 mm (4–8) | 6 mm (4–9) | 0.44    |
| Microsurgical clipping performed| 112 (57%)                        | 20 (32%)                        | <0.0001 |
| Delayed cerebral ischemia       | 69 (35%)                         | 25 (40%)                        | 0.62    |
| Phenytoin use ≥72 hours         | 100 (51%)                        | 27 (43%)                        | 0.33    |
| Levetiracetam use ≥72 hours     | 166 (83%)                        | 50 (79%)                        | 0.43    |
| Seizure before anticonvulsant   | 13 (7%)                          | 8 (13%)                         | 0.20    |
| Seizure after anticonvulsant    | 4 (0.02%)                        | 2 (0.03%)                       | 0.97    |

Data are presented as n (%) unless otherwise stated. SD = standard deviation.

* Included in multivariate analysis.

### Table 5

| Variable                        | Good functional outcome (mRS score ≤3) | Poor functional outcome (mRS score >3) | p value |
|---------------------------------|----------------------------------------|----------------------------------------|---------|
| Age, years, mean ± SD           | 53 ± 12                                | 63 ± 14                                | <0.0001 |
| Female sex                      | 90 (71%)                               | 40 (82%)                               | 0.23    |
| Race                            | 8 (14%)                                | 10 (19%)                               | 0.74    |
| Asian                           | 3 (0%)                                 | 1 (0%)                                 |         |
| Black                           | 8 (14%)                                | 2 (0%)                                 |         |
| Caucasian                       | 107 (20%)                              | 45 (20%)                               |         |
| Hispanic                        | 2 (0%)                                 | 0 (0%)                                 |         |
| Other                           | 6 (12%)                                | 3 (12%)                                |         |
| Smoker                          | 62 (49%)                               | 19 (39%)                               | 0.28    |
| Hypertension history            | 85 (67%)                               | 36 (73%)                               | 0.25    |
| Hunt and Hess grade             | 1 (0%)                                 | 25 (0%)                                | <0.0001 |
| 2                               | 13 (10%)                               | 3 (6%)                                 |         |
| 3                               | 89 (71%)                               | 27 (55%)                               |         |
| 4                               | 24 (19%)                               | 19 (39%)                               |         |
| Intracerebral hematoma          | 18 (14%)                               | 26 (53%)                               | <0.0001 |
| Aneurysm artery location        | 39 (20%)                               | 10 (5%)                                |         |
| Microsurgical clipping performed| 68 (54%)                               | 15 (31%)                               | <0.0001 |
| Delayed cerebral ischemia       | 44 (35%)                               | 19 (39%)                               | 0.76    |
| Phenytoin as anticonvulsant     | 30 (24%)                               | 13 (27%)                               | 0.86    |
| Seizure before anticonvulsant   | 9 (7%)                                 | 7 (14%)                                | 0.15    |
| Seizure after anticonvulsant    | 3 (0.02%)                              | 2 (0.04%)                              | 0.62    |

Data are presented as n (%) unless otherwise stated. mRS = modified Rankin Scale. SD = standard deviation.

* Included in multivariate analysis.
prior to anticonvulsant use were statistically significant associations with DCI in a multivariate logistic regression analysis. The strong association of DCI and delayed infarction with occurrence of seizure prior to anticonvulsant use is a particularly interesting finding. Other studies have reported a similar association between seizures at onset and DCI or poor outcome [19,20]. While the mechanism of such an association is unclear it is possible that seizure at onset following aSAH identifies a part of the brain at risk for focal ischemia, and that more careful monitoring of this subgroup of patients for the occurrence of delayed ischemia may be warranted.

Most importantly, the choice of anticonvulsant was not associated with functional outcome at first follow-up in our study. The multivariate analysis of the subgroup of patients treated with only one anticonvulsant for the duration of the admission was particularly important in this regard, in view of the high rate of crossover from phenytoin to levetiracetam in the overall population. While phenytoin was not associated with worse outcomes compared to levetiracetam in our study, the high rate of crossover suggests that levetiracetam may be the better tolerated agent, or at least more convenient to use. Where a reason for crossover was documented, the most common reasons were fever (a common occurrence following aSAH) and the difficulty with monitoring phenytoin levels and maintaining a “therapeutic” level. The lack of association between phenytoin use and poor outcomes in our study is not necessarily contradictory to the finding of Naidech et al. that cumulative “phenytoin burden” was associated with worse outcomes after aSAH [7]. In the Naidech et al. study, phenytoin burden was studied as a variable, based on daily measurement of serum levels, and patients in the highest quartile of phenytoin burden, specifically, were more likely to have worse outcomes [7]. In contrast, we assessed any use of phenytoin for >72 hours as a variable and did not measure phenytoin “burden”. Our institutional practice of avoiding aggressive supplementation to maintain “therapeutic” serum concentrations of phenytoin on the basis of daily testing of levels may have resulted in a lower overall phenytoin burden. It is possible therefore that higher cumulative phenytoin use over time may be associated with negative cognitive effects, while more judicious use may not be harmful.

Of note, because of our institutional protocol of routinely using anticonvulsant prophylaxis in all patients for the duration of the inpatient admission, the relative benefits or harm of a strategy of using no anticonvulsant prophylaxis, or short-duration anticonvulsant prophylaxis as recommended by some authors [15], could not be evaluated. One study has identified the use of anticonvulsants as a risk factor for poor outcomes following aSAH [21], while another identified no benefit in prevention of seizures in patients undergoing aneurysm repair (including ruptured and unruptured aneurysms) treated with anticonvulsants [22]. While these are potentially important findings, no patients were treated with levetiracetam in the study of aSAH patients [21], and in view of other studies suggesting an increased risk of delayed seizures with short-duration anticonvulsant use [8], further study may be required before universal avoidance of anticonvulsant prophylaxis following aSAH can be recommended as the standard of care.

The major limitation of our study is its retrospective nature. The high crossover rate from phenytoin to levetiracetam limited the sample size of patients treated exclusively with only one anticonvulsant to 175 and may have introduced a selection bias. We did, however, study both the exposure to each anticonvulsant, as well as the exclusive use of levetiracetam versus phenytoin, as risk factors for poor outcome and found no association. The relatively small number of delayed seizures in our study, consistent with other studies [4–6], limited our ability to detect potentially small differences in efficacy between the two anticonvulsants. Patients in our study were not routinely monitored with cEEG, therefore we could not draw conclusions on the effect of anticonvulsant prophylaxis on the occurrence of non-convulsive seizures. Assessments of functional outcome beyond 6 months were not included in our study. Magnesium infusions were routinely used at the same fixed dose in all patients during the period of study; this may have had an effect on the outcomes analyzed, including the rate of seizures. Lastly, although our analysis accounted for common founders, other unmeasured confounders may have been present.

While a higher phenytoin burden may be associated with worse outcomes following aSAH, our study is significant in demonstrating that the routine use of an alternate anticonvulsant, levetiracetam, may not necessarily result in an overall improvement in outcomes. While no difference in outcomes were seen, however, the high crossover rate from phenytoin, along with the equivalent efficacy in seizure prevention seen in our study with levetiracetam, suggests that levetiracetam may in fact be the preferred agent for reasons of tolerance and/or convenience. In the absence of randomized clinical trials in the specific setting of aSAH, levetiracetam may be a reasonable alternative to phenytoin for seizure prophylaxis.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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