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A Randomized Trial of Brief versus Extended Seizure Prophylaxis after Aneurysmal Subarachnoid Hemorrhage

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Abstract

Background—Seizures occur in 10–20% of patients with subarachnoid hemorrhage (SAH), predominantly in the acute phase. However, anticonvulsant prophylaxis remains controversial, with studies suggesting a brief course may be adequate and longer exposure may be associated with worse outcomes. Nonetheless, in the absence of controlled trials to inform practice, patients continue to receive variable chemoprophylaxis. The objective of this study was to compare brief vs. extended seizure prophylaxis after aneurysmal SAH.

Methods—We performed a prospective, single-center, randomized, open-label trial of a brief (three-day) course of levetiracetam (LEV) vs. extended treatment (until hospital discharge). The primary outcome was in-hospital seizure. Secondary outcomes included drug discontinuation and functional outcome.

Results—84 SAH patients had been randomized when the trial was terminated due to slow enrollment. In-hospital seizures occurred in 3 (9%) of 35 in the brief LEV group vs. 1 (2%) of 49 in the extended group ($p=0.2$). 10 (20%) of the extended group discontinued LEV prematurely, primarily due to sedation. Four of five seizures (including one pre-randomization) occurred in patients with early brain injury (EBI) on CT scans (adjusted OR 12.5, 95% CI 1.2–122, $p=0.03$). Good functional outcome (mRS 0–2) was more likely in the brief LEV group (83% vs. 61%, $p=0.04$).

Conclusions—This study was underpowered to demonstrate superiority of extended LEV for seizure prophylaxis, although a trend to benefit was seen. Seizures primarily occurred in those with radiographic EBI, suggesting targeted prophylaxis may be preferable. Larger trials are required to evaluate optimal chemoprophylaxis in SAH, especially in light of worse outcomes in those receiving extended treatment.

Keywords

subarachnoid hemorrhage; seizures; anticonvulsants

INTRODUCTION

Subarachnoid hemorrhage (SAH) from aneurysmal rupture results in significant early brain injury and places patients at risk for both acute seizures and chronic epilepsy [1,2]. A number of studies have suggested that ten percent or more of patients will have a seizure either prior to or during their acute hospitalization [3]. This, in concert with the concern that seizures could have disastrous consequences especially in the setting of an unprotected aneurysm, led to the widespread use of anticonvulsant chemoprophylaxis for patients with SAH. However, some subsequent studies suggested that greater exposure to such drugs (primarily phenytoin) was associated with worse outcomes after SAH, including cognitive dysfunction [4,5]. This fostered uncertainty over the role and optimal duration of seizure prophylaxis after SAH, with some institutions shifting to either a short course of newer agents such as levetiracetam (LEV) or no prophylaxis at all [6,7]. While one retrospective study suggested that a three-day course of phenytoin might be adequate, our own retrospective data suggested that those treated for only three-days (with LEV) had a higher seizure rate than those treated for the duration of their hospital course [8,9].

The Cochrane library recently attempted to evaluate the role of antiepileptic drugs (AEDs) for prevention of seizures after SAH and found no relevant randomized or quasi-randomized studies to answer this important clinical question [10]. Given such clinical equipoise and lack of rigorous prospective data to answer this important practice question, we undertook a randomized comparative effectiveness trial to determine whether an extended course of LEV (until hospital discharge) was superior in preventing in-hospital seizures than a short (three-day) course.

METHODS

The “Duration Of Prophylaxis After Subarachnoid hemorrhage Trial” (DOPAST) was a pragmatic single-center study to compare two prevalent treatment strategies of seizure prophylaxis after SAH: the null hypothesis was that a short course of LEV would be as effective as an extended course. The primary outcome measure was seizures during hospitalization (excluding those prior to randomization). Secondary outcome measures included drug-related adverse events, rates of premature drug discontinuation, with an additional exploratory endpoint of functional outcome (using modified Rankin Scale) on outpatient follow-up.

Eligibility criteria for this study were: 1) aneurysmal SAH; 2) age ≥ 18 years old, with exclusion for: 1) SAH secondary to trauma or other non-aneurysmal cause; 2) early death expected within three days; 3) known allergy to LEV; 4) pregnancy; 5) history of epilepsy on chronic antiepileptic medications. We did not exclude those with seizures or suspected epileptic events at SAH ictus, as these are relatively common, difficult to confirm, and do not definitively confer a greater seizure risk. Eligible SAH patients were approached after aneurysm was secured for enrollment and within three days. Informed consent was obtained from all individual participants included in the study or their legally-authorized representative (LAR). The Human Research Protection Office at our institution approved this study. All procedures performed in studies involving human participants were in

accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The trial was registered at clinicaltrials.gov: NCT01137110 and is reported consistent with the CONSORT guidelines for randomized controlled trials.

Study Protocol

All SAH patients received an initial intravenous loading dose of LEV 1000-mg, usually in the Emergency Department. They were then admitted to the Neuro-ICU for monitoring and continued on LEV 1000-mg BID for three days (adjusted for renal function). If they were enrolled in this study, they were then randomized to discontinue LEV after three days (from admission) or to continue LEV until hospital discharge. Randomization was concealed by selection of sealed opaque envelopes with an equal ratio of brief vs. extended group allocations (in batches of 50). All subjects were followed daily until hospital discharge by a study investigator for clinical seizures (adjudicated by the primary team, with confirmation by the investigator) and adverse drug reactions (ADRs). EEG was performed only as clinically indicated (but was routinely performed in patients with altered or fluctuating mental status) and any seizures detected were included in the primary outcome. While the assessment of seizures was not blinded, functional status at follow-up visit was obtained by raters blinded to group assignment. Based on our prior retrospective data [9], we estimated 8.3% seizure rate in the short duration group compared to 3.4% in the extended duration arm (i.e. approx. 5% absolute effect size); this yielded a required sample size of 400 subjects in order to achieve 60% power.

As part of an exploratory sub-study, we collected clinical data that may be pertinent to seizure risk in this cohort. This included evidence of early brain injury (EBI), defined by radiographic evidence of parenchymal injury on brain imaging performed in the first five days of SAH: this included aneurysm-related intracerebral hemorrhage (ICH), early or procedural infarction, or other visible hypodensity (e.g. retraction injury).

Statistical Analysis

Groups were compared using intention-to-treat analysis. The primary outcome was compared between groups using the Chi-squared test or Fisher exact test. Kaplan-Meier survival analysis was performed on time to seizure (with censoring at hospital discharge), and groups were compared using the log-rank test. We performed logistic regression to evaluate variables associated with in-hospital seizures (combining both pre- and post-randomization events), evaluating the effect of study group as well as variables (including seizure prior to admission, aneurysm clipping, and EBI) found to be associated in univariate analyses. We also used multivariable regression to adjust the effect of study group on functional outcome for other variables found to be associated with outcome (e.g. age, WFNS). Once the study was completed, we also computed a post-hoc actual study power using the observed seizure rates, numbers enrolled, alpha at 0.05 in G*Power (version 3.0).

RESULTS

The study commenced in mid-2010 and was halted in 2014 due to slow enrollment. Figure 1 shows flow of subjects within the study: just over half of 415 total SAH patients admitted to our institution were ineligible, most commonly due to non-aneurysmal cause of SAH, early death or limitation of care, or delayed presentation. Of the 204 eligible, 120 either refused participation, were unable to consent and their LARs either declined or were not available within the time window. A total of 84 subjects were enrolled over four years in the two treatment arms. Randomization was not balanced as the study was stopped mid-way through a block of 50 sealed envelopes, at which point an unequal number of envelopes from one group had been pulled: 49 subjects were enrolled in the extended LEV arm vs. 35 in the short duration LEV arm. No subjects were lost to follow-up prior to termination of study at hospital discharge. 60 subjects were seen in follow-up at between 3-months and 1-year after discharge for evaluation of functional status (median timing of follow-up 5.5 months, IQR 2–6.5 months); incorporating the six who died in-hospital, we had functional outcomes for 68 (81%) of the cohort.

Groups were largely similar except for younger age in the short duration group (Table 1); 14% had a seizure prior to admission in the extended vs. 23% of the short duration arm ($p=0.13$). The extended group received LEV for a median of 14 days (IQR 10–20) compared to 3 days (IQR 2–3) in the brief LEV group. One subject in the brief LEV received more than three days of LEV due to a protocol violation and four additional subjects had LEV restarted for a variety of reasons, including breakthrough seizures or rebleeding. Overall, only 1 subject (2%) of the extended LEV group had an in-hospital seizure compared to 3 subjects (9%) in the group receiving LEV for only three days ($p=0.20$). This difference represents a relative reduction in seizures of 76% and an absolute risk reduction of almost 7%. However, the achieved power given this effect magnitude and sample size was only 0.21. All four seizures occurred after day three, including two seen despite being on LEV (one in the extended group and another in the brief LEV group, but in a patient who had LEV restarted due to fluctuating mental status a few days prior). The other two subjects had LEV restarted after seizures, but no additional AEDs were required for seizure control in any subject. Two subjects did have electrographic seizures in addition to clinical seizures but none had solely subclinical seizures detected in this study. One additional subject had a seizure on the day of aneurysm clipping, but prior to enrollment; this event was not included in the primary study outcome but contributed to the estimate of total in-hospital seizure rate after SAH (i.e. 5 out of 84, 6%).

Survival analysis revealed a separation between groups in seizure freedom after 10–14 days (see Figure 1, $p=0.16$ for difference in groups over time, by log-rank test). 10 of 49 (20%) subjects in the extended LEV group discontinued study drug prior to hospital discharge compared to none in the brief LEV group ($p=0.004$). The most common reason for LEV discontinuation was sedation (in 5 cases). Neither ICU nor hospital length of stay differed between treatment groups (Table 1).

We found that neither baseline clinical nor radiographic SAH scores were associated with in-hospital seizure risk (evaluating all five seizures that occurred, including the one prior to

randomization). Seizures prior to admission (PTA) were not significantly associated with in-hospital seizures (2 of 15, 13% vs. 3 of 67, 5% in those without seizures PTA, $p=0.22$). There was a trend to higher rate of seizures in those who underwent aneurysm clipping (4 of 37, 11%) vs. coiling (1/47, 2%, $p=0.16$). Eighteen (25%) had evidence of early brain injury on head CT: this was stroke (7), ICH (6), SDH (2), and other hypodensity (4). Four of the five patients with seizures had evidence of EBI, which was the only significant predictor of seizures (4/18, 22% vs. 1/52 risk of seizures without EBI). Adjusting for imbalance in clipping and coiling, EBI still conferred a higher risk of seizures (adjusted OR 12.5, 95% CI 1.2–122, $p=0.03$).

Hospital disposition differed significantly between study groups: 33 (94%) of the brief LEV group were discharged home or to rehabilitation compared to 39 (80%) of the extended LEV group ($p=0.06$); this excess was attributable to both a higher in-hospital mortality and more being discharged to long-term care. Of those with follow-up data, 48 (71%) achieved a good recovery, defined as modified Rankin score of 0–2 while 29% only attained mRS 3–6. Age, WFNS grade, and hydrocephalus were all associated with poor outcome. Those with EBI were also more likely to have poor outcome (62% vs. 28%, $p=0.03$) while seizures in-hospital were only weakly associated with worse outcomes ($p=0.18$). Those randomized to the extended LEV group had a trend to higher risk of poor outcome (153/38 vs. 5/30 in brief LEV group, $p=0.04$). After adjusting for age, WFNS, in-hospital seizures, and hydrocephalus, the odds ratio for poor outcome in the extended LEV group was 4.7 (95% CI 1.1–20.2, $p=0.036$).

DISCUSSION

We present the results of DOPAST, the first randomized trial evaluating duration of seizure prophylaxis after SAH. In this small single-center study we compared the effectiveness of a short three-day course of LEV (our standard practice and that espoused by recent guidelines [11]) to an extended course continued until discharge. This trial intended to determine whether there was a benefit to longer seizure prophylaxis, based on some institutional data and clinical concerns that risk of seizures persists throughout the hospital stay and may have deleterious consequences [9,12]. We found a trend to more seizures in those receiving only three days of LEV, although this was primarily driven by two excess late seizures in this group. It is unclear whether extended LEV would have prevented these, as one of these patients had, in fact, been restarted on LEV (off-protocol, by the clinical team) but still had a clinical seizure a few days later despite treatment. The overall rate of in-hospital seizures was only 6% (compared to 18% prior to admission), a pattern concordant with prior literature that seems to suggest that prolonged prophylaxis may be relatively low yield.

Almost all institutions have switched to using newer AEDs (predominantly LEV) in lieu of older agents such as phenytoin, which were associated with more adverse effects including cognitive dysfunction after SAH [4,7,13]. However, despite this study using LEV for chemoprophylaxis, the group receiving treatment throughout their hospital stay had more drug-related adverse events, including a not insignificant proportion (10%) who prematurely discontinued treatment due to sedation. Furthermore, we explored the effect of prolonged LEV exposure on functional recovery after SAH, based on prior reports that greater

anticonvulsant treatment may be associated with worse outcomes [4,5]. Follow-up data was available for a majority (approx. 80%) and demonstrated that the extended LEV group had worse outcomes, even after adjusting for their older age and lower seizure risk. The true implications of this exploratory finding is unclear but gives us pause in recommending that all patients receive LEV throughout their hospital stay.

For this reason, we tried to ascertain which patients were particularly at risk for in-hospital seizures and could therefore benefit more from continued prophylaxis. We found that the presence of radiographic early brain injury (whether hematoma, infarction, or edema on admission or post-operative head CT) was a strong predictor of subsequent seizures. We suggest that extended seizure prophylaxis could be considered in this high-risk group, although confirmatory studies are ideally needed to verify this recommendation. Those without EBI are at low-risk for seizures and could likely have seizure prophylaxis discontinued after aneurysm treatment. A recent non-randomized study found no reduction in seizure risk in those receiving prophylaxis compared to a propensity-matched group not receiving any prophylaxis [14].

This study has a number of significant limitations. We were unable to achieve our target sample size due to slow enrollment. Nonetheless, the sample of SAH patients studied appears comparable to our overall aneurysmal SAH cohort (i.e. on age, gender, racial demographics, baseline SAH severity: based on internal QI data on all aneurysmal SAH admitted from 2014 onward) and, as such, our findings should be broadly generalizable. The actual statistical power we achieved to detect a true difference between groups (given the actual study findings and numbers enrolled) is just over 20%, meaning that it is likely that extended LEV could really provide superior seizure prevention, but we would likely have missed detecting a significant true effect. However, given our finding that those exposed to greater LEV had worse functional outcome, it is unlikely that such a small potential benefit on seizures incidence would be clinically worthwhile when balanced against overall recovery. Projection of these results reveals that between 300 and 350 subjects would have needed to be enrolled to have 80% power to detect an effect. Clearly multi-center collaboration would be needed to perform a study to confirm our preliminary but provocative findings. Such a study might need to either target only high-risk SAH patients (e.g. those with EBI) or include a group randomized to no prophylaxis. DOPAST did not include such a “no prophylaxis” arm given our prior data suggesting excess seizures with shorter prophylaxis.

Furthermore, the study was not blinded (for the primary outcome) which could introduce bias in determining seizures; however, we tried to remain objective by defining seizures based on the clinical team’s determination or confirmation by EEG. Nonetheless, seizures may have been under-detected as EEG monitoring was not performed in all subjects. Given our limited enrollment and exclusion of early deaths, there also may be some selection bias against sicker or higher-risk patients not being enrolled; however, our study still included many poor-grade patients and a high proportion with early/pre-hospital seizures.

CONCLUSION

We were not able to demonstrate superiority of extended seizure prophylaxis after SAH, although a trend was observed. However, larger multi-center trials (focusing not just on seizure risk but functional and cognitive recovery) are needed to determine the optimal seizure prophylaxis, perhaps stratifying by risk factors such as the presence of early brain injury.

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References

1. Claassen J, Peery S, Kreiter KT, et al. Predictors and clinical impact of epilepsy after subarachnoid hemorrhage. *Neurology*. 2003; 60:208–14. [PubMed: 12552032]
2. Huttunen J, Kurki MI, von Und Zu Fraunberg M, et al. Epilepsy after aneurysmal subarachnoid hemorrhage: A population-based, long-term follow-up study. *Neurology*. 2015; 84:2229–37. [PubMed: 25948726]
3. Rhoney DH, Tipps LB, Murry KR, Basham MC, Michael DB, Coplin W. Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. *Neurology*. 2000; 55:258–65. [PubMed: 10908901]
4. Naidech AM, Kreiter KT, Janjua N, et al. Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. *Stroke*. 2005; 36:583–7. [PubMed: 15662039]
5. Rosengart AJ, Huo JD, Tolentino J, et al. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. *Journal of Neurosurgery*. 2007; 107:253–60. [PubMed: 17695377]
6. Dewan MC, Mocco J. Current practice regarding seizure prophylaxis in aneurysmal subarachnoid hemorrhage across academic centers. *J Neurointerv Surg*. 2015; 7:146–9. [PubMed: 24474163]
7. Shah D, Husain AM. Utility of levetiracetam in patients with subarachnoid hemorrhage. *Seizure*. 2009; 18:676–9. [PubMed: 19864168]
8. Chumnanvej S, Dunn IF, Kim DH. Three-day phenytoin prophylaxis is adequate after subarachnoid hemorrhage. *Neurosurgery*. 2007; 60:99–102. discussion –3. [PubMed: 17228257]
9. Murphy-Human T, Welch E, Zipfel G, Diringner MN, Dhar R. Comparison of short-duration levetiracetam with extended-course phenytoin for seizure prophylaxis after subarachnoid hemorrhage. *World Neurosurg*. 2011; 75:269–74. [PubMed: 21492729]
10. Marigold R, Gunther A, Tiwari D, Kwan J. Antiepileptic drugs for the primary and secondary prevention of seizures after subarachnoid haemorrhage. *Cochrane Db Syst Rev*. 2013
11. Lanzino G, D'Urso PI, Suarez J, Participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid H. Seizures and anticonvulsants after aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2011; 15:247–56. [PubMed: 21751102]
12. Sampson TR, Dhar R, Zipfel GJ. Cerebral infarction following a seizure in a patient with subarachnoid hemorrhage complicated by delayed cerebral ischemia. *Surg Neurol Int*. 2011; 2:14. [PubMed: 21427775]
13. Szaflarski JP, Sangha KS, Lindsell CJ, Shutter LA. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care*. 2010; 12:165–72. [PubMed: 19898966]
14. Panczykowski D, Pease M, Zhao Y, et al. Prophylactic Antiepileptics and Seizure Incidence Following Subarachnoid Hemorrhage: A Propensity Score-Matched Analysis. *Stroke*. 2016; 47:1754–60. [PubMed: 27301932]

DOPAST Study Flow Diagram

Figure 1.
CONSORT flow diagram of study participants in DOPAST

Figure 2. Kaplan-Meier survival curve for seizure freedom after randomization (censored at hospital discharge)

Table 1

Characteristics of subjects in two treatment groups

	Brief LEV (n=35)	Extended LEV (n=49)
Age	52 ± 15	60 ± 14 *
Sex, female	23 (66%)	32 (65%)
Race, African-American	9 (27%)	5 (11%)
Weight (kg)	80.5 ± 24	77.1 ± 25
WFNS grade: IV–V	9 (26%)	11 (23%)
Modified Fisher Scale 3–4	17 (52%)	21 (47%)
Seizure prior to admission	8 (23%)	7 (14%)
Aneurysm location: MCA	4 (12%)	9 (19%)
Aneurysm clip/coil	14/21	23/26
Hydrocephalus (EVD)	21 (60%)	29 (60%)
Days of LEV, median (IQR)	3 (2–3)	14 (10–20)
ICU Length of Stay (days)	12 (7–18)	13 (8–17)
Hospital Stay (days)	15 (10–21)	17 (11–22)
mRS 0–2 at follow-up (%)	25/30 (83%)	23/38 (61%) †

* p = 0.008;

† p=0.04