

Seizure Prophylaxis in Aneurysmal Subarachnoid Hemorrhage: Should We Shake it Off?

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November 20, 2015

Learning Objectives

1. Define aneurysmal subarachnoid hemorrhage (aSAH) and basic treatment strategies for the disease state
2. Describe risk factors for seizure occurrence in aSAH
3. Discuss the controversy of prophylactic antiepileptic drug (AED) use in aSAH
4. Analyze and differentiate evidence for and against the use of prophylactic AED therapy in aSAH

I. Aneurysmal Subarachnoid Hemorrhage (aSAH)

A. Definition & anatomy ^[1-3]

1. Aneurysm
 - a. Bulge or ballooning of a blood vessel
 - b. May leak or rupture, causing bleeding into the surrounding area
2. aSAH
 - a. Result of an aneurysm rupture in the brain
 - b. Extravasation of blood into the subarachnoid space

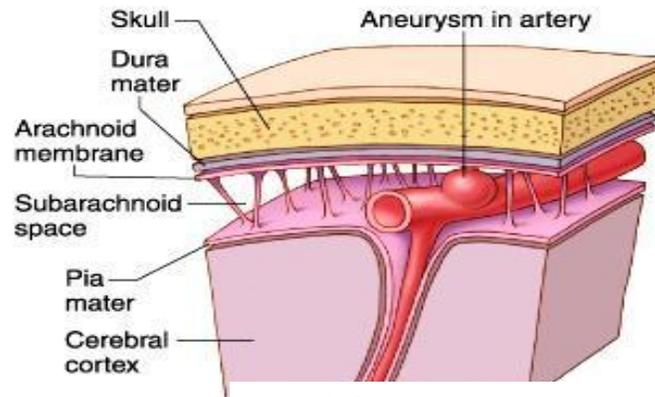


Figure 1. Brain anatomy

B. Incidence ^[1]

1. Incidence varies worldwide
2. United States
 - a. 2-5% of new strokes in the United States
 - b. 14.5 discharges per 100,000 population

C. Risk factors ^[1, 4]

1. Age
2. Women
3. African American
4. Hypertension (HTN)
5. Tobacco use
6. Illicit drug use
7. Heavy alcohol use
8. Family history
9. Large/giant aneurysm (Appendix A)

D. Clinical presentation ^[1, 5]

1. Sentinel headache or “warning leak”
 - a. Stretching of the aneurysm wall
 - b. Small loss of blood from the aneurysm
 - c. Precursor in 50-60% of people with ruptured aneurysms
 - d. Signs and symptoms
 - i. Headache
 - ii. Nausea and vomiting
 - iii. Photophobia
 - iv. Malaise
 - e. Symptoms cease within minutes or hours
 - f. Signifies high risk for aneurysmal hemorrhage within the next two weeks

2. aSAH
 - a. Rupture of aneurysm
 - b. Signs and symptoms
 - i. Severe headache with sudden onset
 - ii. Nausea and vomiting
 - iii. Neck pain
 - iv. Photophobia
 - v. Potential loss of consciousness

II. Diagnosis

- A. Key points ^[1,3]
 1. Confirms presence of cerebral aneurysm
 2. Location and imaging determines most suitable treatment
 3. Failure to obtain appropriate imaging accounts for 70% of misdiagnoses
 4. Initial negative scans should be repeated in 7-10 days
- B. Aneurysm location ^[3]
 1. Determines sensitivity and specificity for detection
 2. Impacts treatment options

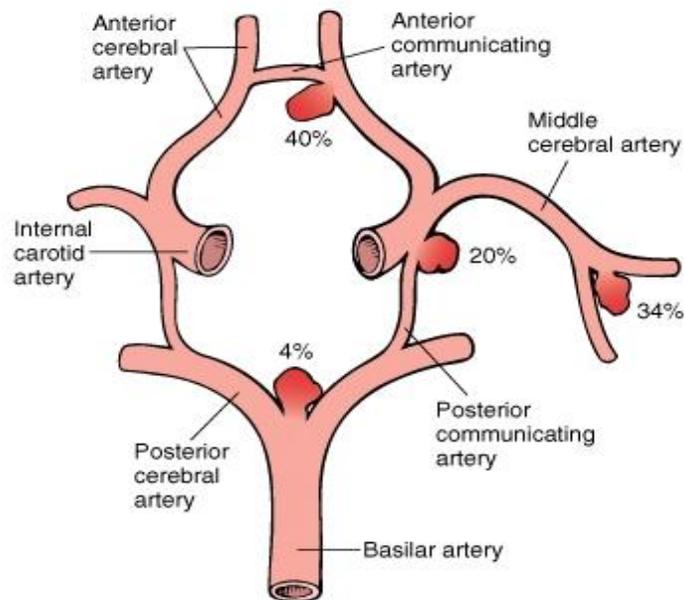


Figure 2. Aneurysm distribution

- C. Non-contrast head computed tomography (CT) ^[3, 6, 7]
1. Cornerstone of diagnosis
 2. Least invasive
 3. Hyperdense areas signify extravasated blood
 4. Reveals additional hematomas, hydrocephalus and cerebral edema
 5. May predict cerebral vasospasm through the extent of blood visualized in subarachnoid and ventricular space
 6. Sensitivity
 - a. 100% during the first 72 hours
 - b. Decreases at 5-7 days

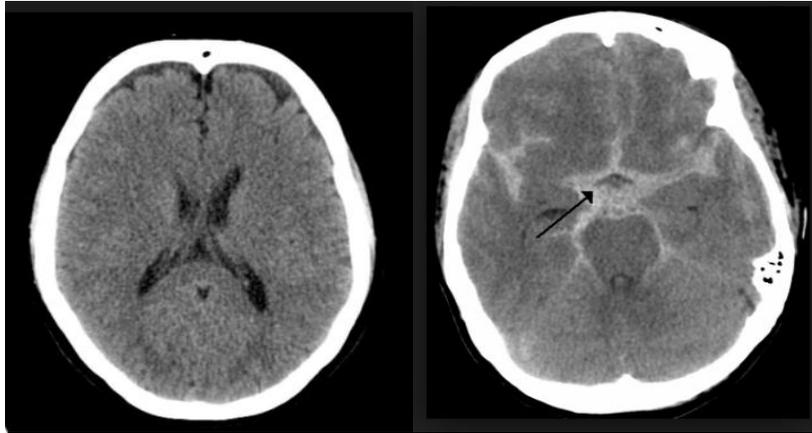


Figure 3. Normal head CT (left) and head CT with subarachnoid hemorrhage (right)

- D. Lumbar puncture (LP) ^[3]
1. Recommended when initial CT is negative
 2. Key diagnostic factors
 - a. May be negative if performed < 2 hours from ictus
 - b. White blood cell (WBC) to red blood cell (RBC) ratio of 1:1000
 - c. Presence of xanthochromia
 - i. Yellow discoloration of cerebrospinal fluid (CSF)
 - ii. Indicates presence of bilirubin
 - iii. Predominantly visually detected
 - iv. Present 2-4 hours post-ictus
- E. CT angiogram (CTA) ^[3, 6, 8]
1. Quick result time
 2. Aneurysms < 3mm may not be visualized
 3. Beneficial in patients who are too unstable to undergo magnetic resonance imaging (MRI)
- F. MRI ^[3]
1. Smaller aneurysms more easily visualized
 2. Better detects blood pigments than non-contrast CT in sub-acute and delayed cases
 3. May be recommended after negative CT, in place of LP
 4. Magnetic resonance angiography (MRA) is a type of MRI utilized to view blood vessels
- G. Digital subtraction angiography (DSA) ^[3, 6, 8]
1. Reference standard for detecting aneurysms
 2. Most accurately determines aneurysm shape due to 3-dimensional presentation
 3. Labor intensive
 4. Expensive
 5. Utilized if CTA and MRI are inconclusive

III. Severity Scales

- A. Hunt & Hess (1968) ^[9]
1. Estimates mortality in non-traumatic subarachnoid hemorrhage (SAH)
 2. Based upon clinical symptoms

Scoring	Definition	Mortality
1	Asymptomatic, mild headache, slight nuchal rigidity	30%
2	Moderate-severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy	40%
3	Drowsiness, confusion, mild focal neurological deficit	50%
4	Stupor, moderate-severe hemiparesis	80%
5	Coma, decerebrate posturing	90%

- B. Fisher Scale (1980) ^[10]
1. Classifies risk of vasospasm
 2. Based upon appearance of aSAH on CT
- C. Modified Fisher Scale (2006) ^[11]
1. More detailed version of the original Fisher Scale
 2. Relates size of bleed with intraventricular involvement

Scoring	Definition	
Scale	Fisher Scale	Modified Fisher Scale
1	No SAH detected	Focal/diffuse thin SAH, no IVH
2	SAH < 1 mm thick	Focal/diffuse thin SAH, with IVH
3	SAH > 1 mm thick*	Thick SAH, no IVH
4	SAH of any thickness with IVH or intraparenchymal hemorrhage	Thick SAH, with IVH*

* Highest risk of vasospasm
IVH = intraventricular hemorrhage

- D. World Federation of Neurological Surgeons (WFNS) Scale (1988) ^[12]
1. Utilized to determine severity of injury and predict patient outcomes
 2. Developed to decrease intraobserver variability

Grade	Motor Deficit	Glasgow Coma Score (Appendix B)
1	Absent	15
2	Absent	13-14
3	Present	13-14
4	Present or absent	7-12
5	Present or absent	3-6

IV. aSAH 2012 Guideline Recommendations

- A. Immediate diagnostic work-up for patients of high suspicion ^[3]
- B. Aneurysm obliteration performed as early as feasible
 - 1. Surgical clipping
 - a. Invasive
 - b. Craniotomy performed
 - c. Metal clip placed at the base of the aneurysm
 - d. Recommendations for use
 - i. Large intraparenchymal hematomas
 - ii. Middle cerebral artery (MCA) aneurysms
 - 2. Endovascular coiling
 - a. Catheter inserted through femoral artery
 - b. Contrast injected to allow viewing of the arteries and exact aneurysm location
 - c. Thin metal wires are placed into the aneurysm space which coil into a mesh ball
 - d. Recommendations for use
 - i. > 70 years old
 - ii. WFNS grade 4 or 5
 - iii. Basilar apex aneurysms
- C. Vasospasm & delayed cerebral ischemia (DCI) ^[3, 13, 14]
 - 1. Vasospasm
 - a. Multifactorial etiology
 - b. Significant stricture of cerebral vessels
 - c. Highest risk 4-14 days after hemorrhage
 - d. Strongly associated with clinical deterioration, cerebral infarction, poor outcome and mortality after aSAH
 - 2. DCI
 - a. Arterial narrowing on angiography
 - b. Increased velocities on transcranial doppler ultrasounds
 - c. May occur in the absence of confirmed vasospasm
 - d. Rate of occurrence
 - i. Ischemia 70%
 - ii. Infarct 20%
 - e. Diagnosis of exclusion
 - 3. Prevention of vasospasm and DCI
 - 1. Nimodipine 60 mg every four hours for 21 days
 - 2. Maintenance of euvolemia
 - 3. Endovascular or surgical treatment within 24 hours of hemorrhage

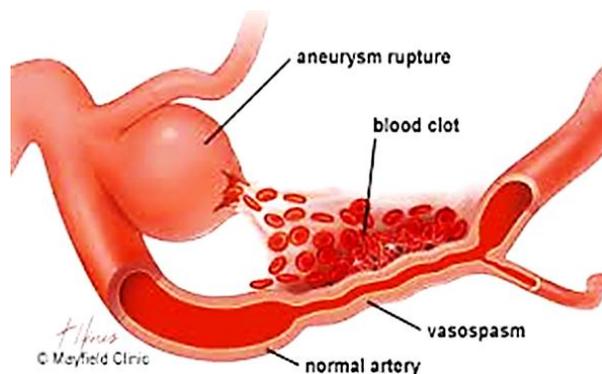


Figure 4. Animation of complications associated with aSAH

D. Hydrocephalus [3, 15, 16]

1. Build-up of CSF in ventricles of the brain
2. Increases intracranial pressure (ICP) leading to potential brain herniation
3. Mechanism is unclear
 - a. Decreased absorption of CSF at the arachnoid granulations
 - b. Ventricular obstruction
4. Management
 - a. Intraparenchymal catheter (IPC)
 - i. Catheter inserted into the parenchyma of the brain
 - ii. Monitors ICP
 - b. External ventricular device (EVD)
 - i. Catheter inserted into the ventricle of the brain
 - ii. Monitors ICP and drains CSF
 - c. Ventriculoperitoneal shunt (VPS)
 - i. Catheter travels from brain ventricles to abdominal cavity
 - ii. Shunts excessive CSF to abdominal cavity
 - iii. Useful in patients with refractory hydrocephalus

E. Rebleeding [3, 17, 18]

1. Risk
 - a. 4% within first 24 hours
 - b. 1-2% per day over the initial 14 days
 - c. 50% during the first 6 months
 - d. 3% per year thereafter
2. Mortality up to 80%
3. Prevention
 - a. Blood pressure control
 - i. Systolic blood pressure (SBP) < 160 mmHg before aneurysm obliteration
 - ii. Consider liberalization after aneurysm obliteration
 - b. Antifibrinolytic therapy
 - i. Recommended for those with unavoidable delay in time to aneurysm obliteration
 - ii. Tranexamic acid or aminocaproic acid
 1. Short-term treatment < 72 hours may be considered
 2. Treatment > 72 hours correlated to increased risk of DCI

F. Seizure [3, 19-21]

1. May develop after initial ictus, after rebleed, or may cause rebleed
2. Occurrence increases disability and mortality risk independent of other complications
3. Risk factors
 - a. Presence of intracerebral hemorrhage
 - b. MCA aneurysm
 - c. HTN
 - d. Ischemia revealed on CT
 - e. Poor neurological grade
 - f. Rebleed
 - g. Thick cisternal blood
 - h. < 40 years old
4. Prevention
 - i. AEDs may be considered in immediate post-hemorrhagic period
 - ii. Long-term AED use is not recommended

V. Seizure Prophylaxis

- A. Background ^[1, 22-25]
 - 1. General definitions
 - a. Immediate seizure: < 1 day of aneurysm rupture
 - b. Early-onset seizure: 1-7 days after aneurysm rupture
 - c. Late-onset seizure: > 7 days after aneurysm rupture
 - 2. Seizure-like episodes occur in up to 26% of all aSAH patients
 - a. Recent studies have presented lower overall incidence of 6-18%
 - b. Majority occur before initial medical evaluation
 - c. Late seizures reported in 3-7%
 - 3. 8% of seizures after aSAH are reported as non-convulsive
 - 4. No level I evidence
 - a. 2013 Cochrane Review
 - i. Inclusion criteria
 - 1. Randomized controlled trials
 - 2. Quasi-randomized controlled trials
 - ii. No articles met inclusion criteria for review
- B. Rationale for prophylaxis ^[1, 24, 26, 27]
 - 1. High risk of permanent neurologic disability
 - 2. Non-convulsive seizure risk
 - 3. Post-hemorrhagic seizures associated with
 - a. Longer intensive care unit stays
 - b. Greater treatment costs
 - c. Increased brain edema
 - d. Increased ICP
 - e. Midline shift
 - f. Decreased functional recovery
- C. Rationale against prophylaxis ^[27, 28]
 - 1. Predominantly data surrounding phenytoin (PHT) studies
 - 2. Use of AEDs currently associated with
 - a. High incidence of in-hospital complications
 - i. Vasospasm
 - ii. DCI
 - iii. Drug-related events and drug-drug interactions
 - 1. Fever
 - 2. Rash
 - 3. CYP interactions
 - b. Poor overall outcome based on GCS and functional status upon discharge

Table 4. Prophylaxis Data

Author	(n)	Population	Endpoints	AED	Conclusions
Baker CJ et al. 1995 [29]	398	Intracranial aneurysms	Need for seizure prophylaxis after craniotomy	<ul style="list-style-type: none"> PHT 94.6% PB 4.1% Other 1.3% 	<ul style="list-style-type: none"> Low incidence of immediate postoperative and long-term seizure disorders If used at all, AED use should only be used in the immediate postoperative time period
Pinto AN et al. 1996 [30]	253	SAH	Incidence of seizure after SAH	<ul style="list-style-type: none"> PHT 	<ul style="list-style-type: none"> Early prophylaxis is reasonable AED use > 1 year is not effective
Byrne JV et al. 2002 [31]	243	aSAH	Need for seizure prophylaxis after coil embolization for aSAH	<ul style="list-style-type: none"> “AED” in 12% 	<ul style="list-style-type: none"> Low incidence of seizures does not justify the use of prophylactic AED therapy
Naidech AM et al. 2005 [21]	527	SAH	PHT burden^	<ul style="list-style-type: none"> PHT 	<ul style="list-style-type: none"> ↑ likelihood of poor functional outcome based on Modified Rankin Scale (Appendix C) ↑ likelihood of poor cognitive outcome Independent predictor of poor outcome
Rosengart AJ et al. 2007# [28]	3552	aSAH	Impact of AEDs on in-hospital complications and outcomes	<ul style="list-style-type: none"> PHT 52.8% PB 18.7% CBZ 2.3% 2x AED 8% 3x AED 0.1% 	<ul style="list-style-type: none"> Prophylactic AED therapy is associated with increased in-hospital complications and worse outcomes
Chou SH et al. 2015* [32]	166	aSAH	Safety and feasibility in early discontinuation of AED	<ul style="list-style-type: none"> PHT 35% LEV 60.1% PB 1.1% 2x AED 3.2% 	<ul style="list-style-type: none"> Early discontinuation associated with ↑ odds of discharge to home ↑ survival to discharge Low rate of angiographic vasospasm occurrence^^

PB = phenobarbital
 CBZ = carbamazepine
 LEV = levetiracetam
 # meta analysis

^ PHT burden = average serum phenytoin level x duration of treatment (max 14 days)

* Excluded patients with “seizure like events” at onset or during early time frame

^^ Not an independent factor

- D. Current trends ^[22, 32]
1. Approximately 65% of all aSAH patients receive seizure prophylaxis
 2. Driven by physician preference
 - a. 2015 survey of 25 large academic centers in the United States
 - i. 52% endorse use of seizure prophylaxis
 - ii. 40% do not routinely use seizure prophylaxis
 - iii. 8% unsure of routine use practices
 - iv. Primary medication choice
 1. 94% LEV
 2. 6% PHT
- E. AED options ^[33, 34]
1. PHT historically used as a primary agent
 2. LEV currently gaining popularity
 3. Other AEDs are reportedly utilized but not studied as primary agents
 - a. Carbamazepime
 - b. Phenobarbital
 - c. Valproic acid

Table 5. Primary AED options ^[33]

	PHT	LEV
Mechanism	<ul style="list-style-type: none"> • Stabilizes neuronal membranes, thereby decreasing seizure activity • Increases efflux or decreases influx of sodium ions across cell membranes in the motor cortex during the generation of nerve impulses 	<ul style="list-style-type: none"> • Inhibition of voltage dependent N-type calcium channels • Facilitation of GABA transmission • Reduction of delayed rectifier potassium current • Binding to synaptic proteins which modulate neurotransmitter release
Kinetics	<ul style="list-style-type: none"> • Non-linear 	<ul style="list-style-type: none"> • Linear
Dosing*	<ul style="list-style-type: none"> • Loading dose: 15 – 20 mg/kg • Initial maintenance dose: 300 mg/day divided TID • Maintenance dose: titrated to therapeutic levels 	<ul style="list-style-type: none"> • Loading dose: 1500 – 2000 mg x1 <ul style="list-style-type: none"> • Weight based: 20 mg/kg x1 • Maintenance dose: 500 – 3000 mg/day divided BID <ul style="list-style-type: none"> • Weight based: 10 mg/kg BID
Monitoring	<ul style="list-style-type: none"> • Total PHT: 10 – 20 mg/L • Free PHT: 1 – 2.5 mg/L 	<ul style="list-style-type: none"> • Not required • 12 – 46 mg/L
Utility in aSAH	<ul style="list-style-type: none"> • Intravenous (IV) administration availability • Demonstrated efficacy in other acute brain injuries 	<ul style="list-style-type: none"> • Good safety profile • Drug monitoring not required • Available in IV formulation • Demonstrated efficacy in treatment of partial-onset seizures • Animal models have shown neuroprotective effects ^[35]
Concerns	<ul style="list-style-type: none"> • Frequently causes adverse drug reactions • Interferes with additional medication metabolism through the CYP450 system • Linked to poor cognitive outcome in patients after SAH • Requires therapeutic drug monitoring (TDM) • TDM complicated by albumin levels 	<ul style="list-style-type: none"> • Not widely studied as monotherapy for seizure prevention in aSAH • Shorter duration of prophylaxis may not be adequate to prevent complications associated with seizure occurrence • ↑ incidence of behavioral abnormalities

*Dosing may vary between institutions

VI. Seizure Prophylaxis Data [24, 26, 27]

Chumnanvej S, Dunn IF, Kim DH. Three-day phenytoin prophylaxis is adequate after subarachnoid hemorrhage. <i>Neurosurgery</i> . 2007; 60(1): 99-103.				
Objective	To evaluate the changes in seizure rate and adverse effects following conversion from a multi-week to a 3-day course of prophylactic PHT for SAH			
Study Design	Single center, retrospective review			
Population	Inclusion		Exclusion	
	<ul style="list-style-type: none"> Spontaneous SAH <ul style="list-style-type: none"> Aneurysmal Arteriovenous malformation Unknown etiology 		<ul style="list-style-type: none"> History of epilepsy Maintenance AED use Traumatic SAH 	
Intervention	Period I: Months 0-9 July 1998 - March 1999		Period II: Months 10-49 April 1999 - June 2002	
	<ul style="list-style-type: none"> 1000 mg loading dose of PHT 100 mg TID maintenance Administered PHT until discharge or development of contraindication <ul style="list-style-type: none"> Allergic reaction Fever of unknown etiology If contraindication developed, patients were switched to carbamazepine 		<ul style="list-style-type: none"> 1000 mg loading dose of PHT 100 mg TID maintenance PHT discontinued 3 days after admission 	
	<ul style="list-style-type: none"> PHT levels were not monitored during either period All patients reviewed at 3 – 12 months after discharge 			
Statistics	<ul style="list-style-type: none"> Analysis of variance to summarize patient demographics Fisher's exact test or χ^2 to compare rates of drug reaction, seizures and mortality 			
Results	<ul style="list-style-type: none"> Baseline characteristics did not differ significantly between groups 			
		Period I	Period II	P-value
		n = 79	n = 370	
	Seizure during hospital stay	1.3%	1.9%	P = 0.603
	Seizure at follow-up	5.7%	4.5%	P = 0.573
	Mortality	32.9%	30.2%	NS
	Hypersensitivity	8.8%	0.5%	P = 0.002
	<ul style="list-style-type: none"> Aneurysm repair completed within 3 days of admission for both groups Period I had 23 patients switch to carbamazepine due to adverse effects Hunt and Hess grades higher in Period II (non-significant) 			
Authors' conclusion	<ul style="list-style-type: none"> Significant decrease in drug complications without an increase in seizure rates Small portion of patients endured a seizure overall (1.9%) Short-course anticonvulsant prophylaxis is adequate after SAH 			

Critique	Advantages	Disadvantages
	<ul style="list-style-type: none"> • Traumatic SAH excluded • Included patients who experienced seizure after SAH • No significant differences in population groups at baseline • Specified subjects who were switched to another AED due to adverse reactions 	<ul style="list-style-type: none"> • Temporal bias • Did not define what was considered a seizure during review • No differentiation of high- or low-risk • Study periods with different population numbers • PHT administration route not specified • Serum levels of PHT were not monitored • Four patients in Period II with a history of epilepsy already on AED maintenance • Duration of PHT in Period I is assumed from hospital LOS average
<p>TID = three times a day NS = not significant LOS = length of stay</p>		

Taylor S, Heinrichs RJ, Janzen JM, Ehtisham A. Levetiracetam is associated with improved cognitive outcome for patients with intracranial hemorrhage. Neurocrit Care. 2011;15(1):80-4.		
Objective	To compare cognitive outcomes in intracranial hemorrhage (ICH) patients receiving seizure prophylaxis with LEV or PHT	
Study Design	Single center, retrospective review	
Population	Inclusion	Exclusion
	<ul style="list-style-type: none"> • Admitted to the neurologic critical care unit between August 2005 and May 2008 • Confirmed ICH based on CT or MRI 	<ul style="list-style-type: none"> • History of dementia • History of seizure disorder • Diagnosed metabolic encephalopathy • Diagnosed sepsis • Admit GCS < 6 (Appendix D)
Intervention	PHT	LEV
	<ul style="list-style-type: none"> • 15-20 mg/kg loading dose • Maintenance dose titrated based on daily PHT levels <ul style="list-style-type: none"> • Target: 1 - 2.5 mcg/ml 	<ul style="list-style-type: none"> • 500-2000 mg/day
	<ul style="list-style-type: none"> • All seizures confirmed through EEG findings 	
Statistics	<ul style="list-style-type: none"> • Ordinal data summarized with medians and interquartile ranges • Continuous data summarized with means and 95% confidence intervals • Categorical data summarized with percentages • Differences in patients receiving LEV versus PHT using Mann-Whitney U exact, independent samples t-test, and Fisher exact test • Relationships between baseline characteristics and clinical outcomes using multivariate logistic and ordinal regression models 	

Results	<ul style="list-style-type: none"> Hemorrhage types <ul style="list-style-type: none"> Intracerebral hemorrhage (47%) SAH (30.6%) Subdural hemorrhage (22.4%) Baseline characteristics did not differ significantly between groups 			
		PHT	LEV	P-value
		n=25	n=60	
	Mean GCS at discharge	11 (IQR 8.8-15)	14 (IQR 11-15)	P = 0.023
	Discharged home	16%	21.7%	P = 0.04
	Seizure during hospital stay	8%	0%	P = 0.03
	“Intact” cognitive function at discharge	36%	56.7%	P = 0.08
	<ul style="list-style-type: none"> Multivariate logistic regression to show a significant effect on seizure incidence dependent on drug group (P= 0.038) 			
Authors’ conclusion	<ul style="list-style-type: none"> Patients treated with LEV exhibit better cognition at discharge than patients treated with PHT LEV patients had a statistically significant decrease in seizure incidence and were discharged with better cognitive function 			
Critique	Advantages		Disadvantages	
	<ul style="list-style-type: none"> Did not exclude patients with seizure on presentation No significant differences in baseline characteristics Clinical seizures verified by electroencephalogram Accounted for discharge destinations as a factor of cognitive and functional ability 		<ul style="list-style-type: none"> Retrospective chart review Patients with GCS < 6 excluded 30% of patients were SAH patients Variation in baseline ICH scores No mention of duration of treatment for either study population No mention of administration route Therapeutic attainment of PHT not discussed Specific LEV dosing strategy not discussed No follow-up after discharge 	

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. <i>World Neurosurg.</i> 2011;75(2):269-74.		
Objective	To determine if the switch to a short course of LEV leads to increased frequency of in-hospital seizures, especially those occurring after day three, compared with a traditional regimen of extended-course phenytoin	
Study Design	Single center, retrospective review	
Population	Inclusion	Exclusion
	<ul style="list-style-type: none"> Admitted to the neurology/neurosurgery intensive care unit between January 2003 and December 2008 Diagnosis of spontaneous SAH 	<ul style="list-style-type: none"> < 18 years old AED before admission Hospital length of stay < 5 days

Intervention	PHT		LEV	
	<ul style="list-style-type: none"> • 15 mg/kg loading dose with maintenance doses based of PHT levels or occurrence of seizures • Enteral maintenance PHT for duration of hospital stay • PHT levels monitored at least once weekly • Patients could be switched to LEV if they experienced a drug-related adverse event or had breakthrough seizures 		<ul style="list-style-type: none"> • 500 mg twice daily for three days • Initiated intravenously, with enteral doses for maintenance if able • Treatment extended if patient had a seizure within the first three days of hospital stay or at the discretion of the neurosurgical team 	
<p>In-hospital seizures were defined as ‘early’ or ‘late’</p> <ul style="list-style-type: none"> • Pre-hospital seizure: before or on the day of admission • Early seizure: On or before day three of hospital admission • Late seizure: From day three to hospital discharge 				
Statistics	<ul style="list-style-type: none"> • Chi-square or Fisher exact tests for proportional data • Mann-Whitney U tests for continuous data • Student t-test for age • Binary logistic regression used for association determination between groups and in-hospital seizures 			
Results	<ul style="list-style-type: none"> • Baseline characteristics did not differ significantly between groups 			
		PHT	LEV	P-value
		n = 297	n = 145	
	Duration of treatment (days)	13.7	3.6	
	Pre-hospital seizure	8.8%	4.84%	P = 0.14
	In-hospital seizure	3.45%	8.3%	P = 0.026
	Early seizure	1.4%	2.8%	P = 0.45
	Late seizure	2.0%	5.5%	P = 0.049
		No in-hospital seizure	In-hospital seizure	P-value
		n = 420	n = 22	
	ICU median LOS	14 (IQR 10-19)	18.5 (IQR 13-22)	P = 0.005
	Hospital LOS	19 (IQR 13-25)	27 (IQR 21-33)	P = 0.001
	Early seizure		36%	
	Late seizure		64%	
<ul style="list-style-type: none"> • Adjustment for age, clinical grade, history of prior seizure, and aneurysm treatment concluded increased likelihood of in-hospital seizure with LEV (odds ratio 2.3; P=0.054) • 40% of PHT patients switched to LEV during AED course (mean 8.5 days from admission) • No increased mortality rate with PHT <ul style="list-style-type: none"> • Death or discharge to nursing home was not significantly different, but did trend higher in PHT group (P=0.06) • Excess late seizure in LEV group (P=0.04) 				
Authors’ conclusion	<ul style="list-style-type: none"> • The use of short-duration LEV for seizure prophylaxis after spontaneous SAH was associated with a higher rate of in-hospital seizures than an extended course of PHT • Particularly related to seizure occurrence after the initial three day period 			

Critique	Advantages	Disadvantages
	<ul style="list-style-type: none"> • Specified administration routes for AEDs • Statistical analysis on AED groups as well as between seizure and non-seizure groups • PHT doses adjusted based on TDM • Differentiation between early and late seizures • Specified concurrent treatment complications that may have increased risk of seizure occurrence • Identified flaws in dosing strategies during discussion • Detailed reasoning for changes in AED therapy during hospital stay 	<ul style="list-style-type: none"> • Excluded data from patients with death or discharge before hospital day five • Only 53% of patients had confirmatory head CT • No EEG monitoring available to rule out non-convulsive seizures • No LEV loading dose utilized • Daily dosing of LEV on the lower end of recommended dosing • Patients analyzed with their original AED group even if medication was changed due to side effects • No data on long-term functional and cognitive outcomes • Higher rate of seizures seen in the LEV group than in previous studies

VII. Summary of Evidence

- A. Studies surrounding the use of seizure prophylaxis in aSAH are retrospective
- B. PHT has been a primary option for aSAH seizure prophylaxis primarily due to IV formulation availability
- C. Safety concerns with PHT
 - 1. Concern for increased complications during hospital stay
 - 2. Increased adverse effects due to drug interactions and narrow therapeutic index
 - 3. Long-term cognitive impairment, relative to the dose and duration of PHT used
- D. Introduction of new AEDs have sparked interest for use in aSAH
- E. Short-term (three-day) LEV treatment durations have not been shown to be effective in preventing seizures in aSAH
- F. Prospective studies have yet to be accomplished on this subject

VIII. Conclusions

- A. The decision to provide seizure prophylaxis is a balance of considerations
 - 1. Adverse effects of antiepileptic therapy
 - 2. Overall risk of developing seizures
 - 3. Perceived implications of seizure on medical management
- B. Safe and effective drug profiles of relatively new AEDs allow further consideration for prophylactic treatment in this ICH subtype
- C. Duration of seizure prophylaxis in aSAH should be approached on a case by case basis

IX. Recommendations

- A. Prophylaxis should be initiated in patients under the following conditions
 - 1. Hunt & Hess Grade 4 or 5
 - 2. Fisher Grade III or IV
 - 3. Modified Fisher Grade II-IV
 - 4. Concomitant intracerebral hemorrhage
 - 5. MCA aneurysm
 - 6. History of hypertension
- B. AED
 - 1. LEV
 - a. Good adverse effect profile
 - b. No TDM required
 - c. Correlated to beneficial outcomes
 - 2. Dosing
 - a. Load: 20 mg/kg IV infusion
 - b. Maintenance: 10 mg/kg twice daily IV or enteral
- C. Duration
 - 1. Initiate immediately upon diagnosis or strong suspicion of aSAH
 - 2. Total duration 8 days
 - 3. Consider prolonged duration if seizure occurs during hospital stay

X. Appendices

Appendix A: Aneurysm Size Classification ^[4]

Aneurysm Size Classification	
Classification	Size (mm)
Small	< 11
Medium	11-25
Giant	> 25

Appendix B: Glasgow Coma Scale ^[36]

Glasgow Coma Scale		
Category	Response	Score
Eye(s) Opening	Spontaneous	4
	To speech	3
	To pain	2
	No response	1
Verbal	Oriented to time, place, person	5
	Confused/disoriented	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best Motor Response	Obeys commands	6
	Move to localized pain	5
	Flexion withdraws from pain	4
	Abnormal flexion (decorticate)	3
	Abnormal extension (decerebrate)	2
	No response	1

Appendix C: Modified Rankin Scale ^[37]

Modified Rankin Scale	
Score	Description
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attending to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

XI. References

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