Anticonvulsant in aneurysmal subarachnoid hemorrhage

Concerns over the possible consequences of a seizure in the setting of an unsecured intracranial aneurysm, has led to routine prophylactic administration of antiepileptic drugs (AEDs) following SAH in many centers [1) 2)].

In a review, the Department of Clinical Pharmacy, University of Tennessee Health Science Center, College of Pharmacy, Knoxville, describes the evidence associated with the use of AEDs for seizure prophylaxis in patients with intracerebral tumors, traumatic brain injury, aneurysmal subarachnoid hemorrhage, craniotomy, ischemic stroke, and intracerebral hemorrhage. Clear evidence indicates that the short-term use of AEDs for seizure prophylaxis in patients with traumatic brain injury and aneurysmal subarachnoid hemorrhage may be beneficial; however, evidence to support the use of AEDs in other disease states is less clear [3)].

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 [4)].

Current practice regarding seizure prophylaxis in aneurysmal subarachnoid hemorrhage across academic centers

An eight question survey was sent to 25 US centers with high volume aSAH cases (>100 annually). Respondents were asked about institutional practices regarding use, duration, and type of seizure prophylaxis.

13 (52%) respondents endorsed the utility of seizure prophylaxis while 10 (40%) did not, and two (8%) were unsure. Among respondents using prophylaxis, levetiracetam was the firstline medication for the majority (94%) while phenytoin was used as a primary agent at one (4%) center and as a secondary agent at four (16%) centers. Duration of levetiracetam prophylaxis ranged from 1 day to 6 weeks following SAH (mean 13.2; median 11). Only a single center employed EEG routinely in all aSAH patients but most supported EEG use when the neurologic examination was unreliable or inexplicably declining. 24 (96%) respondents agreed that a trial randomizing patients to levetiracetam or no antiseizure medication is warranted at this time, and all 25 (100%) believed that such a trial would be appropriate or ethically sound.

The routine use of seizure prophylaxis following aSAH is controversial. Among a sampling of 25 major academic centers, most administer prophylaxis, while a significant proportion does not. The majority believes a trial randomizing patients to receive seizure prophylaxis is both timely and ethical [5)].

Complications

Literature has suggested increased adverse effects associated with post-hemorrhagic AED exposure; including serious drug related complications as well as worse cognitive and functional outcomes [6)].

Up to 21% of those receiving AED prophylaxis suffered adverse medication side effects, including impaired liver function, thrombocytopenia, rash, and Stevens-Johnson syndrome. Few studies to date have specifically evaluated prophylactic AED treatment protocols, and only one has detailed the incidence and risk factors of clinical seizures in patients not receiving prophylactic AED medications [7)].

Reviews

2013

Raper et al. performed a MEDLINE (1985-2011) search to identify randomized controlled trials and retrospective series of aSAH. Statistical analyses of categorical variables such as presentation and early and late seizures were carried out using χ(2) and Fisher exact tests.

They included 25 studies involving 7002 patients. The rate of early postoperative seizure was 2.3%. The rate of late postoperative seizure was 5.5%. The average time to late seizure was 7.45 months. Patients who experienced a late seizure were more likely to have MCA aneurysms, be Hunt/Hess grade III, and be repaired with microsurgical clipping than endovascular coiling.

Despite improved microsurgical techniques and antiepileptic drug prophylaxis, a significant proportion of patients undergoing aneurysm clipping still experience seizures. Seizures may occur years after aneurysm repair, and careful monitoring for late complications remains important. Furthermore, routine perioperative AED use does not seem to prevent seizures after SAH [8)].

Marigold et al. searched the Cochrane Epilepsy Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 1) in The Cochrane Library, and MEDLINE (1946 to 12th March 2013). We checked the reference lists of articles retrieved from these searches.

They considered all randomised and quasi-randomised controlled trials in which patients were assigned to a treatment (one or more AEDs) or placebo.

Two review authors (RM and JK) independently screened and assessed the methodological quality of the studies. If studies were included, one author extracted the data and the other checked it.

No relevant studies were found.

There was no evidence to support or refute the use of antiepileptic drugs for the primary or secondary prevention of seizures related to subarachnoid haemorrhage. Well-designed randomised controlled trials are urgently needed to guide clinical practice [9)].

2011

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

with longer-term treatment [10].

2010

The objective was addressed through the development of a critically appraised topic that included a clinical scenario, structured question, search strategy, critical appraisal, assessment of results, evidence summary, commentary, and bottom line conclusions. Neurology consultants and residents, a medical librarian, clinical epidemiologists, and content experts in the fields of epilepsy, neurosurgery, and critical care contributed to the review and placed the evidence in clinical context.

There were no relevant randomized, controlled trials that addressed the question. A post hoc analysis of data from 4 trials of tirilazad for aSAH showed that prophylactic AED therapy was associated with worse Glasgow Outcome Scale scores at 3 months (odds ratio 1.56, 95% confidence interval 1.16-2.10; P = 0.003) but numerous confounders limit data interpretation.

There are insufficient data to support or refute the prophylactic use of AED therapy after aSAH. Randomized, controlled trials are needed to address the efficacy and risks of AEDs in this setting and should take into account factors such as aneurysmal factors (location, hemorrhage grade, degree of parenchymal injury), type of aneurysm surgery (clip vs. coil), and evaluate the timing and duration of AED use [11].

Case series

2017

Human et al. performed a prospective, single-center, randomized, open-label trial of a brief (3-day) course of levetiracetam (LEV) versus extended treatment (until hospital discharge). The primary outcome was in-hospital seizure. Secondary outcomes included drug discontinuation and functional outcome.

Eighty-four SAH patients had been randomized when the trial was terminated due to slow enrollment. In-hospital seizures occurred in three (9%) of 35 in the brief LEV group versus one (2%) of 49 in the extended group (p = 0.2). Ten (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 computed tomography (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).

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 [12].

2016

Panczykowski et al.retrospectively analyzed a prospectively collected database of subarachnoid

hemorrhage patients admitted to the Department of Neurological Surgery, University of Pittsburgh Medical Center,

Between 2005 and 2007, all patients received prophylactic AEDs upon admission. After 2007, no patients received prophylactic AEDs or had AEDs immediately discontinued if initiated at an outside hospital. A propensity score-matched analysis was then performed to compare the development of clinical and electrographic seizures in these 2 populations.

Three hundred and fifty three patients with spontaneous subarachnoid hemorrhage were analyzed, 43% of whom were treated with prophylactic AEDs upon admission. Overall, 10% of patients suffered clinical and electrographic seizures, most frequently occurring within 24 hours of ictus (47%). The incidence of seizures did not vary significantly based on the use of prophylactic AEDs (11 versus 8%; P=0.33). Propensity score-matched analyses suggest that patients receiving prophylactic AEDs had a similar likelihood of suffering seizures as those who did not (P=0.49).

Propensity score-matched analysis suggests that prophylactic AEDs do not significantly reduce the risk of seizure occurrence in patients with spontaneous subarachnoid hemorrhage [13].

2014

Current guidelines recommend against the use of phenytoin following aneurysmal subarachnoid hemorrhage (aSAH) but consider other anticonvulsants, such as levetiracetam, acceptable. The objective of Karamchandani 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 [14].

2013

Exploratory analysis was performed on 413 patients enrolled in CONSCIOUS-1 (Clazosentan to Overcome Neurological Ischemia and Infarction Occurring after Subarachnoid Hemorrhage), a prospective randomized trial of clazosentan for the prevention of angiographic vasospasm. The association among clinical, laboratory, and radiographic covariates and the occurrence of seizures

following SAH were determined. Covariates with a significance level of $p < 0.20$ on univariate analysis were entered into a multivariate logistic regression model. Receiver operating characteristic (ROC) curve analysis was used to define optimal predictive thresholds.

Of the 413 patients enrolled in the study, 57 (13.8%) had at least 1 seizure following SAH. On univariate analysis, a World Federation of Neurosurgical Societies grade of IV-V, a greater subarachnoid clot burden, and the presence of midline shift and subdural hematomas were associated with seizure activity. On multivariate analysis, only a subarachnoid clot burden (OR 2.76, 95% CI 1.39-5.49) and subdural hematoma (OR 5.67, 95% CI 1.56-20.57) were associated with seizures following SAH. Using ROC curve analysis, the optimal predictive cutoff for subarachnoid clot burden was determined to be 21 (of a possible 30) on the Hijdra scale (area under the curve 0.63).

A greater subarachnoid clot burden and subdural hematoma are associated with the occurrence of seizures after aneurysm rupture. These findings may help to identify patients at greatest risk for seizures and guide informed decisions regarding the prescription of prophylactic anticonvulsive therapy. Clinical trial registration no.: NCT00111085 (ClinicalTrials.gov) [15].

2008

A total of 137 adult patients were enrolled in this two-year retrospective study. Baseline prognostic variables were analyzed based on Cox's proportional hazards model after a minimum of one-year follow-up.

Seizures occurred in 21 patients who had SAH, including acute symptomatic seizures in 11.7% (16/137) and unprovoked seizures in 3.6% (5/137). None progressed to status epilepticus during hospitalization. After a minimum of one-year follow-up, the mean Glasgow Outcome Score was 3.5 +/- 1.4 for patients with seizures and 3.1 +/- 1.1 for those without.

Higher mean World Federation of Neurological Societies grade on presentation was predictive of seizure, but seizure itself was not a significant prognostic predictor after a minimum of one-year follow-up. Regarding potential side effects of anti-epileptic drugs, anti-epileptic therapy should be carefully administered to patients with seizures after aneurysmal SAH [16].

2007

Rosengart et al. examined data collected in 3552 patients with SAH who were entered into four prospective, randomized, double-blind, placebo-controlled trials conducted in 162 neurosurgical centers and 21 countries between 1991 and 1997. The prevalence of AED use was assessed by study country and center. The impact of AEDs on in-hospital complications and outcome was evaluated using conditional logistic regressions comparing treated and untreated patients within the same study center.

Antiepileptic drugs were used in 65.1% of patients and the prescribing pattern was mainly dependent on the treating physicians: the prevalence of AED use varied dramatically across study country and center (intraclass correlation coefficients 0.22 and 0.66, respectively [$p < 0.001$]). Other predictors included younger age, worse neurological grade, and lower systolic blood pressure on admission. After adjustment, patients treated with AEDs had odds ratios of 1.56 (95% confidence interval [CI] 1.16-2.10; $p = 0.003$) for worse outcome based on the Glasgow Outcome Scale; 1.87 (95% CI 1.43-2.44; $p < 0.001$) for cerebral vasospasm; 1.61 (95% CI 1.25-2.06; $p < 0.001$) for neurological

deterioration; 1.33 (95% CI 1.01-1.74; p = 0.04) for cerebral infarction; and 1.36 (95% CI 1.03-1.80; p = 0.03) for elevated temperature during hospitalization.

Prophylactic AED treatment in patients with aneurysmal SAH is common, follows an arbitrary prescribing pattern, and is associated with increased in-hospital complications and worse outcome [17].

From July 1998 to June 2002, 453 patients with spontaneous subarachnoid hemorrhage were treated. In the first 9 months, 79 patients were administered PHT until discharged from the hospital, unless a drug reaction occurred first. In the last 39 months, PHT was discontinued 3 days after admission (370 patients), unless there was a history of epilepsy (four patients). This study represents a retrospective analysis of prospectively collected data, with follow-up periods of 3 to 12 months after discharge. RESULTS: The 3-day PHT regimen produced a statistically significant reduction (P = 0.002) in the rate of PHT complications. In the first period, seven (8.8%) out of 79 patients experienced a hypersensitivity reaction, compared with two (0.5%) out of 370 patients in the second period. The percentage of patients having seizures, both short- and long-term, did not change significantly. In the first period, the seizure rate during hospitalization was 1.3%; in the second period, it was 1.9% (P = 0.603). At an average follow-up period of 6.7 months, three (5.7%) out of 53 survivors in the first period experienced a seizure (including those who had a seizure during hospitalization). In the second period, 12 (4.6%) out of 261 survivors experienced a seizure at an average follow-up period of 5.4 months (P = 0.573).

A 3-day regimen of PHT prophylaxis is adequate to prevent seizures in subarachnoid hemorrhage patients. Drug reactions are significantly reduced, but seizure rates do not change. Short-term PHT administration may be a superior treatment paradigm [18].

2005

Naidech et al. studied 527 SAH patients and calculated a “PHT burden” for each by multiplying the average serum level of PHT by the time in days between the first and last measurements, up to a maximum of 14 days from ictus. Functional outcome at 14 days and 3 months was measured with the modified Rankin scale, with poor functional outcome defined as dependence or worse (modified Rankin Scale > or =4). We assessed cognitive outcomes at 14 days and 3 months with the telephone interview for cognitive status. RESULTS: PHT burden was associated with poor functional outcome at 14 days (OR, 1.5 per quartile; 95% CI, 1.3 to 1.8; P<0.001), although not at 3 months (P=0.09); the effect remained (OR, 1.6 per quartile; 95% CI, 1.2 to 2.1; P<0.001) after correction for admission Glasgow Coma Scale, fever, stroke, age, National Institutes of Health Stroke Scale > or =10, hydrocephalus, clinical vasospasm, and aneurysm rebleeding. Seizure in hospital (OR, 4.1; 95% CI, 1.5 to 11.1; P=0.002) was associated with functional disability in a univariate model only. Higher quartiles of PHT burden were associated with worse telephone interview for cognitive status scores at hospital discharge (P<0.001) and at 3 months (P=0.003). CONCLUSIONS: Among patients treated with PHT, burden of exposure to PHT predicts poor neurologic and cognitive outcome after SAH [19].

2000

Rhoney et al. reviewed 95 SAH patient charts using standardized forms. Variables included

prophylaxis duration, seizure incidence and timing, CT findings, AED adverse events, and 1-year patient follow-up.

Prehospital seizures occurred in 17.9% (17/95) of patients; another 7.4% (7/95) had a questionable prehospital seizure. In-hospital seizures occurred in 4.1% (4/95) of patients, a mean of 14.5 +/- 13.7 days from ictus; three of these four patients were receiving an AED at the time of seizure. Inpatient AED were prescribed to 99% of the cohort for a median of 12 (range 1 to 68) days. Approximately 8% of the cohort had posthospital discharge seizures; this included the patients who had prehospital or in-hospital seizures, 50% of whom were receiving AED therapy at the time of the seizure. Adverse effects occurred in 4. 1%; none were serious. The thickness of cisternal clot was associated with having a seizure; no other clinical predictors were identified. Having a seizure at any time did not adversely affect outcome.

In this SAH population, the majority of seizures happened before medical presentation. In-hospital seizures were rare and occurred more than 7 days postictus for patients receiving AED prophylaxis. The vast majority of putative clinical predictors did not help predict the occurrence of seizures; only the thickness of the cisternal clot was of value in predicting seizures. Patient selection for and the efficacy and timing of AED prophylaxis after SAH deserve prospective evaluation [20].

Experimental Studies

A study demonstrated that Valproic Acid (VPA) improves neurological outcome and decreases brain injury in a mouse model of SAH [21].

Recommendations

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[1], [18]
Chumnanvej S, Dunn IF, Kim DH. Three-day phenytoin prophylaxis is adequate after subarachnoid hemorrhage. Neurosurgery. 2007 Jan;60(1):99-102; discussion 102-3. PubMed PMID: 17228257.
[2], [8]
Raper DM, Starke RM, Komotar RJ, Allan R, Connolly ES Jr. Seizures after aneurysmal subarachnoid hemorrhage: a systematic review of outcomes. World Neurosurg. 2013 May-Jun;79(5-6):682-90. doi: 10.1016/j.wneu.2012.08.006. Epub 2012 Sep 25. Review. PubMed PMID: 23022642.
[3]
Rowe AS, Goodwin H, Brophy GM, Bushwitz J, Castle A, Deen D, Johnson D, Lesch C, Liang N, Potter E, Roels C, Samaan K, Rhoney DH; Neurocritical Care Society Pharmacy Section. Seizure prophylaxis in neurocritical care: a review of evidence-based support. Pharmacotherapy. 2014;34(4):396-409. doi: 10.1002/phar.1374. Epub 2013 Nov 26. Review. PubMed PMID: 24277723.
[4], [12]
Human T, Diringer MN, Allen M, Zipfel GJ, Chicoine M, Dacey R, Dhar R. A Randomized Trial of Brief Versus Extended Seizure Prophylaxis After Aneurysmal Subarachnoid Hemorrhage. Neurocrit Care. 2017 Aug 22. doi: 10.1007/s12028-017-0440-5. [Epub ahead of print] PubMed PMID: 28831717.
[5]

Dewan MC, Mocco J. Current practice regarding seizure prophylaxis in aneurysmal subarachnoid hemorrhage across academic centers. J Neurointerv Surg. 2015 Feb;7(2):146-9. doi: 10.1136/neurintsurg-2013-011075. Epub 2014 Jan 28. PubMed PMID: 24474163.

6) , 19)

Naidech AM, Kreiter KT, Janjua N, Ostapkovich N, Parra A, Commichau C, Connolly ES, Mayer SA, Fitzsimmons BF. Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. Stroke. 2005 Mar;36(3):583-7. Epub 2005 Jan 20. PubMed PMID: 15662039.

7) , 16)

Lin YJ, Chang WN, Chang HW, Ho JT, Lee TC, Wang HC, Tsai NW, Tsai MH, Lu CH. Risk factors and outcome of seizures after spontaneous aneurysmal subarachnoid hemorrhage. Eur J Neurol. 2008 May;15(5):451-7. doi: 10.1111/j.1468-1331.2008.02096.x. Epub 2008 Mar 5. PubMed PMID: 18325027.

9)

Marigold R, Günther A, Tiwari D, Kwan J. Antiepileptic drugs for the primary and secondary prevention of seizures after subarachnoid haemorrhage. Cochrane Database Syst Rev. 2013 Jun 5;(6):CD008710. doi: 10.1002/14651858.CD008710.pub2. Review. PubMed PMID: 23740537.

10)

Lanzino G, D'Urso PI, Suarez J; Participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Seizures and anticonvulsants after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011 Sep;15(2):247-56. doi: 10.1007/s12028-011-9584-x. Review. PubMed PMID: 21751102.

11)

Riordan KC, Wingerchuk DM, Wellik KE, Zimmerman RS, Sirven JI, Noe KH, Patel BM, Demaerschalk BM. Anticonvulsant drug therapy after aneurysmal subarachnoid hemorrhage: a critically appraised topic. Neurologist. 2010 Nov;16(6):397-9. doi: 10.1097/NRL.0b013e3181efc92f. PubMed PMID: 21150393.

13)

Panczykowski D, Pease M, Zhao Y, Weiner G, Ares W, Crago E, Jankowitz B, Ducruet AF. Prophylactic Antiepileptics and Seizure Incidence Following Subarachnoid Hemorrhage: A Propensity Score-Matched Analysis. Stroke. 2016 Jul;47(7):1754-60. doi: 10.1161/STROKEAHA.116.013766. Epub 2016 Jun 14. PubMed PMID: 27301932; PubMed Central PMCID: PMC4927347.

14)

Karamchandani RR, Fletcher JJ, Pandey AS, Rajajee V. Incidence of delayed seizures, delayed cerebral ischemia and poor outcome with the use of levetiracetam versus phenytoin after aneurysmal subarachnoid hemorrhage. J Clin Neurosci. 2014 Sep;21(9):1507-13. doi: 10.1016/j.jocn.2014.03.009. Epub 2014 Jun 3. PubMed PMID: 24919470.

15)

Ibrahim GM, Fallah A, Macdonald RL. Clinical, laboratory, and radiographic predictors of the occurrence of seizures following aneurysmal subarachnoid hemorrhage. J Neurosurg. 2013 Aug;119(2):347-52. doi: 10.3171/2013.3.JNS122097. Epub 2013 Apr 12. PubMed PMID: 23581590.

17)

Rosengart AJ, Huo JD, Tolentino J, Novakovic RL, Frank JI, Goldenberg FD, Macdonald RL. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. J Neurosurg. 2007 Aug;107(2):253-60. PubMed PMID: 17695377.

20)

Rhoney DH, Tipps LB, Murry KR, Basham MC, Michael DB, Coplin WM. Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. Neurology. 2000 Jul 25;55(2):258-65. PubMed PMID: 10908901.

21)

Tso MK, Lass E, Ai J, Loch Macdonald R. Valproic Acid treatment after experimental subarachnoid

hemorrhage. Acta Neurochir Suppl. 2015;120:81-5. doi: 10.1007/978-3-319-04981-6_14. PubMed PMID: 25366604.