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Prophylactic Use of Anti-Epileptic Drugs in Patients with Spontaneous Intracerebral Hemorrhage

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Abstract

Background—The effect of prophylactic antiepileptic drugs (AEDs) on mortality and functional outcome in patients with intracerebral hemorrhage (ICH) is uncertain.

Methods—We used data from the Virtual International Stroke Trials Archive (VISTA) to evaluate the effect of prophylactic AEDs on ICH outcome. Uni- and multivariate logistic and Cox regression models were designed to determine the impact of prophylactic AEDs on mortality and disability, defined as a modified Rankin Scale (mRS) >3, at 90 days following ICH.

Results—Of 802 patients with ICH, 81 (10%) received prophylactic AEDs. Patients who received AED prophylaxis had higher ICH volume (median 23.2 [interquartile range: 10.5–38.0] vs. 14.3 [7.1–27.0] cm³, $p=0.001$), and ICH score (1 [0–2] vs. 1 [0–1], $p=0.03$). In univariate analyses, AED prophylaxis was associated with higher probability of mRS >3 at 90 days (62% vs. 49%, $p=0.03$) and a trend towards increased mortality (27% vs. 18%, $P=0.06$). Although seizure did not influence ICH outcome, any AED prophylaxis and phenytoin use in particular were both associated with mRS >3 at 90 days (OR 1.66 [1.04–2.66], $p=0.03$ for any AED; OR 1.97 [1.06–3.67], $p=0.03$ for phenytoin prophylaxis) in univariate analyses. After adjustment for components of the ICH score, none of these associations remained significant.

Conclusion—Patients with higher ICH scores and larger hemorrhages are more likely to receive prophylactic AEDs. We found no independent effect of prophylactic AED treatment on outcome after ICH.

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* Appendix

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Authors' Contributions:

AZ reviewed the literature, did the statistical analysis, and wrote the primary draft of the manuscript. SM, BC, and MM made substantial contributions to the conception and design and to the analysis and interpretation of the data. SK conceived the idea, designed the study and finalized the manuscript. All the authors read and approved the final version.

Keywords

Intracerebral hemorrhage; anti-epileptic drugs; outcome; mortality

Introduction

Intracerebral hemorrhage (ICH) comprises 10-15 % of stroke cases and has the highest rate of mortality and morbidity.^{1,2} Despite this, there are no proven treatments and ambiguity exists in many areas of ICH management such as seizure prophylaxis.¹

Seizure is a common complication after ICH and is reported in 2% to 40% of ICH patients.³⁻¹¹ The wide variation in the estimates of seizure incidence among different studies can be attributed to several factors, including duration and mode (clinical vs. electrographic) of monitoring, length of follow-up and patient characteristics. Moreover, there is substantial uncertainty in the impact of seizure on outcome. Seizure is reported to be linked to worsening of stroke severity, midline shift, rebleeding, and pneumonia, all potentially contributing to worse outcomes.^{4,10,12} Further, seizure may have adverse effects on autonomic function and blood pressure.^{1,13} Conversely, several studies failed to identify an independent association between seizure and poor outcome and one study reported better functional outcome in post-ICH seizure patients.^{3,6,10,12,14}

There are also conflicting data about the use of antiepileptic drugs (AEDs) in ICH patients. Some studies reported that AEDs may decrease post-ICH seizure but others failed to show such an effect.^{10,15,16} Since post-ICH seizure may not be associated with ICH outcome, preventing seizures would not necessarily improve morbidity or mortality of ICH, and AEDs might have other effects that could be harmful.^{9,17} For instance, in a prospective study, phenytoin was associated with fever and worse functional outcome, although its administration did not modify seizure risk.⁹ Current guidelines recommend against AEDs as a prophylactic therapy after ICH based on these studies, though they are small and imprecise.¹ The aim of the current study was to evaluate the impact of seizure and AED use on mortality and functional outcome in a large cohort of well-characterized ICH patients.

Methods

Study population

We used data from the Virtual International Stroke Trials Archive (VISTA, (www.vista.gla.ac.uk/)). VISTA is a joint project collecting data from multiple clinical trials for exploratory analyses. Complete details about the VISTA database have been published previously.¹⁸ We built on our existing analyses of the CHANT trial¹⁷ by extending this sample to include accumulating trial data from VISTA-ICH. We obtained VISTA data derived from randomized clinical trials in which patients with ICH were enrolled, underwent baseline CT, and were followed for 90 days. We limited our cohort to subjects with Glasgow Coma Scale (GCS) recorded on arrival, mRS at 90 days, post-ICH seizure, and concomitant AED use. We excluded subjects with brain tumor, aneurysm, vascular malformation, head trauma, hematological malignancy, hemophilia or history of epilepsy.

Data collection

Data on the demographic characteristics of subjects, administration of AEDs, and development of seizure, were collected. All patients were followed until death or 90 days, whichever was first. ICH volume was measured using either Analyze Software (Overland Park, KS, US) or estimated using the ABC/2 formula.¹⁹ Further, data about location of hemorrhage and presence of intraventricular hemorrhage (IVH) were collected. The geographical regions in which subjects were enrolled were divided into these areas: Africa, Australia and New Zealand, North America, Central and South America, Europe, Western Asia, and Eastern and South-Eastern Asia.

The ICH score was used as a method of risk stratification.²⁰ It is a 6-point calculation based on five indicators: age, GCS at arrival, ICH volume and location of hematoma, and the presence of intraventricular extension. The ICH score has been validated to predict mortality and disability after ICH.²¹ Prophylactic AED treatment was defined as administration of any AED within the first 7 days after ICH and prior to any record of seizure. Functional outcome at 90 days was measured by modified Rankin Scale (mRS), and poor functional outcome was defined as mRS>3.

Statistical analysis

Analysis was carried out using SPSS 17.0 statistical analysis software (SPSS Inc., Chicago, 2008). Mann-Whitney U test, Chi-square or Fisher exact test were used to compare characteristics of patients according to seizure and AED prophylaxis status, as appropriate. Several univariate logistic and Cox regression models were designed to evaluate factors influencing ICH outcome, reflected by either death or mRS>3 at 90 days. Further, using multivariate logistic and Cox models, the impact of AED prophylaxis on ICH outcome was evaluated after adjustment for possible confounding factors. Ordered logistic models were designed to evaluate shift of mRS in patients who received prophylactic AEDs. The overall ICH score as a single summary variable or its component as distinct variables were included in the multivariate models in order to determine whether prophylactic AEDs independently affect the ICH outcome. The effects of specific AEDs (phenytoin or other) on ICH outcome were evaluated using similar regression models. Finally, since it is possible that seizures at onset of ICH were not reliably recorded in the study documentation, the aforementioned analyses were repeated after exclusion of patients who received AEDs within 24 hours following ICH onset in order to confirm the effect of AEDs used solely prophylactically. In all analyses, $P<0.05$ was considered significant.

The sample size was determined by the availability of data from VISTA. Prior to receiving the data for analysis, we estimated that about 10% of subjects would have received a prophylactic AED and that about 40% of subjects without AED treatment would have a poor outcome. Based on these assumptions and allowing for a type I error probability of 0.05, we estimated a power of 80% to detect an odds ratio of at least 2.0 for poor outcome after AED use.

Results

A total of 802 patients were available for analysis. Median age (interquartile range [IQR]) of subjects was 66 (IQR 56-75) years. Most were enrolled from European (455 patients, 57%) and North American (226 patients, 28%) centers. Among 81 (10%) patients who received AEDs, most (89%) received a single AED. The median time of prophylactic AED initiation after ICH was 1 day (IQR 1-2). The most common prophylactic AEDs were phenytoin (47 patients, 58%), and valproate (14 patients, 17%). During the follow-up period, 155 (19%) patients died, and 405 (50%) had mRS>3. The median mRS at 90 days was 4 (2-5).

Table 1 compares the characteristics of patients by seizure status. Baseline characteristics of both groups were similar, and prophylactic AEDs were given to 10% and 13% of patients without and with subsequent seizure, respectively. Prophylactic AEDs did not have effect on the development of seizure (Odds Ratio [OR] 1.38, 95%CI: 0.31-6.22). Seizures were not significantly associated with outcome at 90 days.

Characteristics of patients according to prophylactic AED use are presented in Table 2. Subjects who received AED prophylaxis had higher ICH volume (median 23.2 cm³, IQR 10.5-38.0 cm³ vs. 14.3 cm³, IQR 7.1-27.0 cm³, $p=0.001$) and higher ICH score (median 1, IQR 0-2 vs. 1, IQR 0-1, $p=0.03$). Prophylactic AEDs were administered more commonly in North America compared to other regions (20% vs. 6%, $p<0.001$) and less commonly in Europe compared to elsewhere (5% vs. 17%, $p<0.001$). Despite wide disparity in prophylactic AED administration in these regions, there were no significant differences between North America and other regions in mortality (20.4% vs. 18.9%) or poor functional outcome (51.3% vs. 50.2%), nor between Europe and elsewhere in mortality (21.5% vs. 16.4%) or poor functional outcome (52.5% vs. 47.8%).

In univariate analyses, AED prophylaxis was associated with higher probability of mRS>3 at 90 days (62% vs. 49%, $p=0.03$) and a trend towards increased mortality (27% vs. 18%, $p=0.06$, Table 2). Without adjustment, prophylactic AEDs overall and phenytoin in particular appeared to be associated with worse functional outcome defined by mRS>3 (OR 1.66, 95%CI:1.04-2.66, $p=0.03$ for any AED and OR 1.97, 95%CI:1.06-3.67, $p=0.03$ for phenytoin, Table 3). ICH score components (except infratentorial hemorrhage) and total scores were strongly associated with both mortality and mRS>3. After adjustment for ICH score components (Table 3), the relationships between AEDs and outcomes were completely attenuated, with no effect of prophylactic AEDs on disability (OR 1.33, 95%CI:0.78-2.26) or mortality (Hazard Ratio [HR] 1.14, 95%CI:0.72-1.80). Similar results were obtained with adjustment for the total ICH score. The point estimates suggested that phenytoin was more likely to be associated with worse outcomes than any AED, but still no significant difference was detected. Figure 1 shows the effect of AED administration on distribution of mRS scores before and after adjustment for ICH score, as the main prognostic factor of ICH outcome. In univariate shift analysis, AED prophylaxis was associated with worse mRS (OR 1.60 95%CI:1.06-2.41, $p=0.03$), but significance was lost after adjustment for ICH score (OR 1.40 95%CI: 0.91-2.17).

In a sensitivity analysis to attempt to account for patients that may have had a seizure prior to enrollment, we performed similar uni- and multivariate regression models excluding 12 subjects who received AED prophylaxis within 24 hours after ICH onset (Table 4). Similar to the main analyses, in unadjusted models, administration of any AED and in particular phenytoin appeared to increase the risk of poor outcome for any AED (OR 1.81; 95% CI: 1.09-3.03, $p=0.02$) and for phenytoin (OR 2.20; 95% CI: 1.09-4.43, $p=0.03$). After controlling for either ICH score components or overall ICH score, AEDs were no longer associated with ICH outcome (Table 4).

Discussion

The current study demonstrates that neither prophylactic AED treatment nor seizure after ICH is independently associated with mortality or functional recovery. We found that patients with more severe ICH, as measured by higher ICH scores, were more frequently treated with prophylactic AEDs, and this likely resulted in confounding by indication. The prospective cohort data within VISTA provided an opportunity to explore this issue and adjust for these factors.

There is a wide discrepancy in opinion regarding the use of prophylactic AEDs and there is no general consensus about its indications.²² For instance, the proportion of ICH patients who receive prophylactic AEDs ranges from 20% to over 80% in various studies.^{7,9,10,15,16} In a survey of physicians who manage ICH patients, 33% responded that they never administer prophylactic AEDs while 9% said they always do.²² Our data, derived from multicenter trials, identified a notable global disparity in AED use among regions, with North American centers prescribing prophylactic AEDs more commonly than the rest of the world, yet without a difference in clinical outcomes.

Prior studies have evaluated the impact of AEDs in patients with ICH or other similar medical conditions with conflicting results. A post-hoc analysis of 295 subjects from an international randomized ICH trial demonstrated that prophylactic AED use was independently associated with poor functional outcome.¹⁷ In a single center prospective study of 98 subjects, phenytoin prophylaxis was associated with fever which may have contributed to poor outcome after ICH.⁹ Similarly, a meta-analysis involving over 3500 patients with spontaneous subarachnoid hemorrhage (SAH) found that AED use was associated with increased in-hospital complications and worse outcome, with phenytoin as the most commonly used AED.²³ Prophylactic phenytoin has also been reported to suppress functional outcome after traumatic brain injury.²⁴ The potentially deleterious effects of phenytoin have been attributed to inflammatory pathways that play an important role in post-ICH brain injury.^{25,26} In an *in vitro* model of inflammation, phenytoin reduced the glial viability and altered microglial activation.²⁷ In the present study, phenytoin was the most frequently used AED and appeared harmful in the unadjusted models, but this negative effect was completely attenuated after controlling for confounding factors.

Other AEDs may have different effects on ICH outcome. In a prospective cohort, no effect on ICH outcome was observed after administration of levetiracetam.⁹ In the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study, around 40% of 744 patients received

AED prophylaxis, with levetiracetam being by far the most commonly administrated AED (around 90% of AED treated patients). In that study, no significant effect was attributed to AED prophylaxis after adjustment for possible confounding variables.²⁸ Another study showed that levetiracetam reduced mortality risk after lobar ICH, but phenytoin did not.²⁹ Patients may have been treated with different AEDs because of other clinical selection factors. One small randomized double blind clinical trial has been published comparing prophylactic valproic acid to placebo in 72 ICH patients.³⁰ In that study, prophylactic valproic acid did not reduce the risk of subsequent seizure, but was associated with better neurological outcome after one year.³⁰ We had insufficient power to detect effects specific to other AEDs but overall there seemed to be no relationship between these other agents and ICH outcome.

There is also wide variation in the reported frequency of post-ICH seizure, with some studies reporting rates as low as 2-3%.^{11,31} Our estimate (1.8%) is close to the lowest values reported in these prior studies. Long-term follow-up and/or EEG monitoring might result in detection of a higher rate of post-ICH seizure. Further, patients with very early onset seizure may not have been enrolled in clinical trials. Patients with very severe hemorrhages, including those with low GCS, may also have been excluded, yet they may also be the patients at highest risk of post-ICH seizure.^{7,12,32} The median GCS in our dataset was 15 (13-15) and the 90 day mortality rate was only 19%, suggesting that relatively few had severe ICH. These differences may at least partly contribute to the low incidence of seizure in our patients and may limit the generalizability of our results. In general agreement with several prior studies, we found no effect of prophylactic AEDs on the incidence of seizure after ICH.^{15,16}

Although seizure could theoretically exacerbate ICH due to sudden changes in blood pressure, intracranial pressure, and metabolic demand,^{13,33,34} we did not find significant association between seizure and ICH outcome. Of note, several other studies are consistent with our results. For example, in a retrospective cohort study, seizure did not influence functional ICH outcome after over 3 years follow-up.³¹ Likewise, in a prospective multicenter study, seizure was not associated with 30-day or 1-year mortality risk.³ A recently published population-based study suggested that occurrence of seizure 24 hours after ICH onset predicts better outcome.¹² Thus, it may be reasonable to suggest that prevention of seizure *per se* may not improve ICH outcome and should not be a priority in acute care.

A number of strengths and limitations of the current study merit discussion and consideration. The major strength of this study is that we analyzed a sizable number of ICH patients from various geographical regions. Because the subjects were participating in clinical trials, the data were collected prospectively, including all concomitant medications and adverse events, and were subject to monitoring and verification. All patients were followed for at least 90 days which allowed us to have a consistent estimate regarding the effects of AEDs on ICH outcome. The major limitation, relevant to our results interpretation, is the *post hoc* study design. Seizure was not the primary outcome of these trials and was only identified if recorded as an adverse event, though most previous studies have used similar designs. Although this is one of the largest cohorts of patients with ICH, we may not

have adequate power to rule out potentially meaningful harmful effects of either seizure or prophylactic AEDs. Further, clinical trials often exclude the most acutely ill patients, and our results may not apply to them. We also did not have reliable data on the use of anticoagulants prior to ICH, which is a robust predictor of poor outcome. Finally, there may be important heterogeneity in patient management among centers, regions, and trials that we could not explore further within this specific dataset. Notably, we did not have data on do-not-resuscitate orders.

In summary, we found that patients with more severe ICH are more likely to be selected for treatment with prophylactic AEDs. After accounting for ICH severity, neither prophylactic AED use nor seizure after onset were independently associated with ICH outcome. There is also substantial variability in the pattern of AED use in different global regions, which may at least partly explain the variability in the results of previous reports. Ultimately, randomized trials are needed to rigorously evaluate the advantages and disadvantages of prophylactic AEDs for ICH.

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Figure 1.

The unadjusted calculated distribution of mRS at day 90 (A), and after adjustment for the total ICH score (B).

Table 1

Univariate Analysis by Seizure

	No seizure (n=787)	With seizure (n=15)	<i>p</i> values
Age, years	66 (56-75)	65 (45-78)	0.78
Sex, No of male subjects (%)	504 (64)	11 (73)	0.46
GCS	15 (13-15)	14 (13-15)	0.67
ICH volume, cm ³	15.1 (7.4-29.0)	9.5 (6.5-21.0)	0.44
IVH, No (%)	248 (31)	6 (40)	0.58
Infratentorial hemorrhage, No (%)	30 (4)	0 (0)	1.00
Lobar hemorrhage, No (%)	473 (60)	11 (73)	0.30
ICH score	1 (0, 1)	1 (0, 2)	0.71
AED, No (%)	79 (10)	2 (13)	0.66
Phenytoin, No (%)	45 (6)	2 (13)	0.22
Valproate, No (%)	14 (2)	0 (0)	1.00
Levetiracetam, No (%)	3 (0)	0 (0)	1.00
Carbamazepine, No (%)	6 (1)	0 (0)	1.00
Multiple AEDs, No (%)	8 (1)	1 (7)	0.16
Geographical region			
Africa, No (%)	6 (1)	0 (0)	1.00
Europe, No (%)	447 (57)	8 (53)	0.80
North America, No (%)	221 (28)	5 (33)	0.77
South America, No (%)	4 (1)	0 (0)	1.00
Western Asia, No (%)	6 (1)	0 (0)	1.00
Eastern and South-Eastern Asia, No (%)	73 (9)	1 (7)	1.00
Australia, No (%)	30 (4)	1 (7)	0.45
Outcome measures			
Mortality, No (%)	150 (19)	5 (33)	0.18
mRS>3, No (%)	397 (50)	8 (53)	0.82

Continuous variables are presented as mean±SD or median (IQR).

Table 2

Univariate Analysis by AED Prophylaxis

	No AED prophylaxis (n=721)	AED prophylaxis (n=81)	p value
Age, years	66 (56-75)	64 (56-78)	0.92
Sex, No of male subjects (%)	465 (64)	50 (62)	0.62
GCS	15 (13-15)	14 (12-15)	0.12
ICH volume, cm ³	14.3 (7.1-27.0)	23.2 (10.5-38.0)	0.001
IVH, No (%)	224 (31)	30 (37)	0.27
Infratentorial hemorrhage, No (%)	30 (4)	0 (0)	0.06
Lobar hemorrhage, No (%)	432 (60)	52 (64)	0.45
ICH score, Units	1 (0, 1)	1 (0, 2)	0.03
Geographical region			
Africa, No (%)	4 (1)	2 (2)	0.11
Europe, No (%)	432 (60)	23 (28)	<0.001
North America, No (%)	181 (25)	45 (56)	<0.001
South America, No (%)	4 (1)	0 (0)	1.00
Western Asia, No (%)	5 (1)	1 (1)	0.47
Eastern and South-Eastern Asia, No (%)	66 (9)	8 (10)	0.83
Australia, No (%)	29 (4)	2 (2)	0.76
Outcome measures			
Mortality, No (%)	133 (18)	22 (27)	0.06
mRS>3, No (%)	355 (49)	50 (62)	0.03

Continuous, ordinal and categorical variables are presented as mean±SD or median (IQR).

Table 3

Unadjusted and Multivariate-Adjusted Outcomes

	Mortality Hazard ratio	<i>p</i> value	mRS>3 Odds ratio	<i>p</i> value
Univariate models				
Age, years	1.05 (1.03-1.06)	<0.001	1.05 (1.04-1.06)	<0.001
Age 80 years	2.99 (2.10-4.27)	<0.001	3.76 (2.30-6.13)	<0.001
GCS	0.77 (0.72-0.81)	<0.001	0.70 (0.64-0.77)	<0.001
GCS 5-12 ^a	2.44 (1.74-3.41)	<0.001	3.33 (2.27-4.91)	<0.001
GCS 3-4 ^a	329 (62-1734)	<0.001	----	
ICH volume, cm ³	1.033 (1.028-1.038)	<0.001	1.05 (1.04-1.06)	<0.001
ICH volume 30 cm ³	4.90 (3.57-6.79)	<0.001	5.66 (3.82-8.40)	<0.001
IVH	4.90 (3.57-6.73)	<0.001	2.70 (1.97-3.68)	<0.001
Infratentorial hemorrhage	1.50 (0.74-3.05)	0.26	1.12 (0.54-2.34)	0.75
Lobar hemorrhage	1.79 (1.26-2.54)	<0.001	1.36 (1.02-1.80)	0.03
ICH Score				
1 ^b	3.99 (2.26-7.05)	<0.001	3.54 (2.52-4.96)	<0.001
2 ^b	9.64 (5.43-17.1)	<0.001	13.1 (7.88-21.8)	<0.001
3 ^b	18.8 (9.72-36.2)	<0.001	22.9 (7.85-66.8)	<0.001
4 ^b	49.2 (21-113)	<0.001	----	
Seizure	1.85 (0.76-4.51)	0.18	1.12 (0.40-3.13)	0.83
AED	1.52 (0.97-2.39)	0.07	1.66 (1.04-2.66)	0.03
Phenytoin	2.12 (1.28-3.50)	0.004	1.97 (1.06-3.67)	0.03
Other AEDs	0.74 (0.30-1.81)	0.51	1.25 (0.63-2.50)	0.52
Multivariate adjusted models				
Adjusted for components of ICH score				
AED	1.14 (0.72-1.80)	0.58	1.33 (0.78-2.26)	0.29
Phenytoin	1.33 (0.80-2.23)	0.27	1.36 (0.67-2.76)	0.39
Adjusted for overall ICH score				
AED	1.19 (0.76-1.87)	0.45	1.41 (0.84-2.39)	0.20
Phenytoin	1.44 (0.87-2.40)	0.16	1.51 (0.75-3.04)	0.24

Hazard and odds ratios are reported for presence of a condition or for each one unit increase in the value of a variable. Hazard ratios are reported for prediction of death within 90 days after ICH and odds ratios are estimated for mRS>3 at 90 days.

^a13 GCS 15 as the reference group.

^bICH=0 as the reference group.

Table 4

Unadjusted and Multivariate-Adjusted Outcomes, After Exclusion of Subjects Who Received AEDs within 24hrs after ICH

	Mortality Hazard ratio	p value	mRS>3 Odds ratio	p value
Univariate models				
AED	1.54 (0.95-2.50)	0.08	1.81 (1.09-3.03)	0.02
Phenytoin	2.14 (1.23-3.70)	0.007	2.20 (1.09-4.43)	0.03
Other AEDs	0.83 (0.34-2.02)	0.68	1.37 (0.66-2.84)	0.39
Multivariate adjusted models				
Adjusted for components of ICH score				
AED	1.23 (0.76-2.00)	0.39	1.55 (0.87-2.76)	0.13
Phenytoin	1.48 (0.85-2.59)	0.17	1.73 (0.78-3.84)	0.18
Adjusted for overall ICH score				
AED	1.31 (0.81-2.12)	0.27	1.64 (0.93-2.90)	0.09
Phenytoin	1.64 (0.94-2.85)	0.08	1.91 (0.87-4.18)	0.11

Hazard and odds ratios are reported for presence of a condition or for each one unit increase in the value of a variable. Hazard ratios are reported for prediction of death within 90 days after ICH and odds ratios are estimated for mRS>3 at 90 days.