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Prophylactic Antiepileptic Drug Use and Outcome in the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) Study

Kevin N. Sheth, MD¹, Sharyl R. Martini, MD, PhD², Charles J. Moomaw, PhD³, Sebastian Koch, MD⁴, Mitchell S. V. Elkind, MD, MS⁵, Gene Sung, MD, MPH⁶, Steven J. Kittner, MD, MPH⁷, Michael Frankel, MD⁸, Jonathan Rosand, MD, MSc.⁹, Carl D. Langefeld, PhD¹⁰, Mary E. Comeau, MA¹⁰, Salina Waddy, MD¹¹, Jennifer Osborne, RN, BSN³, and Daniel Woo, MD, MS³ for the ERICH Investigators

¹Department of Neurology, Yale University School of Medicine, New Haven, CT

²Department of Neurology, Baylor College of Medicine, Houston TX

³Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati OH

⁴Department of Neurology, University of Miami School of Medicine, Miami FL

⁵Department of Neurology, College of Physicians and Surgeons, Columbia University, New York NY

⁶Department of Neurology, University of Southern California, Los Angeles CA

⁷Department of Neurology, University of Maryland School of Medicine, Baltimore MD

⁸Department of Neurology, Emory University School of Medicine, Atlanta GA

⁹Department of Neurology, Massachusetts General Hospital, Boston, MA

¹⁰Department of Biostatistical Sciences and Center for Public Health Genomics, Wake Forest School of Medicine. Winston-Salem NC

¹¹National Institute of Neurological Disorders and Stroke, Bethesda MD

Corresponding Author: Kevin N. Sheth, MD, 15 York Street, LCI 1003, New Haven, CT 06510, kevin.sheth@yale.edu, Telephone: 443-615-4729.

KNS and SRM contributed equally to this work.

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Sharyl Martini – none

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Gene Sung – NINDS

Steven Kittner – NINDS

Michael Frankel – NINDS

Jonathan Rosand – NINDS

Carl Langefeld – NINDS

Mary Comeau – NINDS

Salina Waddy – NINDS

Jennifer Osborne – NINDS

Daniel Woo – NINDS

Abstract

Background and Purpose—The role of antiepileptic drug (AED) prophylaxis following intracerebral hemorrhage (ICH) remains unclear. This analysis describes prevalence of prophylactic AED use, as directed by treating clinicians, in a prospective ICH cohort and tests the hypothesis that it is associated with poor outcome.

Methods—Analysis included 744 ICH patients enrolled in the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study prior to November 2012. Baseline clinical characteristics and AED use were recorded in standardized fashion. ICH location and volume were recorded from baseline neuroimaging. We analyzed differences in patient characteristics by AED prophylaxis, and we used logistic regression to test whether AED prophylaxis was associated with poor outcome. The primary outcome was 3 month modified Rankin Scale score, with 4–6 considered poor outcome.

Results—AEDs were used for prophylaxis in 289 (39%) of the 744 subjects; of these, levetiracetam was used in 89%. Patients with lobar ICH, craniotomy, or larger hematomas were more likely to receive prophylaxis. Although prophylactic AED use was associated with poor outcome in an unadjusted model (OR=1.40; 95% CI=1.04–1.88; p=0.03), this association was no longer significant after adjusting for clinical and demographic characteristics (OR=1.11; 95% CI=0.74–1.65; p=0.62).

Conclusions—We found no evidence that AED use (predominantly levetiracetam) is independently associated with poor outcome. A prospective study is required to assess for a more modest effect of AED use on outcome following ICH.

Keywords

Intracerebral hemorrhage; stroke; seizure; critical care

Introduction

Intracerebral hemorrhage (ICH) is the most devastating stroke subtype.¹ There is continued uncertainty regarding several aspects of acute management, including evaluation and management of seizures and the utility of seizure prophylaxis.² Although seizures are common after ICH, the role of prophylactic antiepileptic drugs (AED) is controversial. In patients with ICH, however, AED use has been associated with worse functional and cognitive outcome.³ Prior reports commonly used phenytoin, and data on other anticonvulsants are limited.^{3, 4} As such, NINDS has identified the impact and role of AED use after ICH as an important knowledge gap.⁵ This analysis was designed to test the hypothesis that prophylactic AED use is associated with worse functional outcome after ICH.

Methods

Source Sample, Seizure History, and AED Use

Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study methods have been previously described.⁶ Case report forms and baseline interviews included prior seizure

history and AED use prior to ICH onset; medications, doses, and durations of AED administration during the hospital stay; and whether the agent was given for prophylaxis or seizure treatment. AED administration was at the discretion of treating physicians.

In order to isolate the impact of *prophylactic* AED use on outcome, subjects were excluded for seizures in the acute setting, taking an AED appropriate for epilepsy during the two weeks prior to onset, and missing documentation. Subjects without Glasgow Coma Score (GCS) or location, volume, and intraventricular (IVH) presence from CT data were also excluded. Because poor outcome was defined as 3 month mRS score 4,³ patients with pre-onset mRS scores of 4 or 5, as well as those lost to follow up, were excluded.

Statistical Analysis

Demographic and clinical characteristics were tested for differences among ethnicities and AED prescription using Wilcoxon rank sum test and chi square tests for contingency tables. Univariate and multivariate logistic regression models estimated the odds ratio (OR) and 95% confidence interval (CI) for associations of AED use with patient characteristics and tested for association with poor outcome at 3 months. A stepwise logistic regression model (forward selection with backward elimination) was computed with entry and exit criteria of $p=0.05$. Collinearity and variance inflation diagnostics evaluated model assumptions.

Power analysis estimated the odds ratio for AED use and worse outcome detectable with 0.80 and 0.99 power, given our sample size⁷. Power analysis with type 1 error rate $\alpha=0.05$ gives 0.80 power to detect worse outcome associated with AED prophylaxis at an OR=1.5 (an effect 15.6% of that previously reported³), and 0.99 power to detect an OR=2.0.

Results

Description of the analytic cohort

We analyzed data for the first 1143 ERICh study patients who presented to emergency departments at enrolling sites between 10/13/2010 and 10/30/2012. Cases were excluded for the following (not mutually exclusive) reasons: seizure in the acute setting ($n=101$), AED use during the two weeks prior to onset ($n=37$), missing documentation regarding AED in the acute setting ($n=8$), GCS unavailable ($n=29$), neuroimaging data unavailable ($n=98$), pre-onset mRS of 4 or 5 ($n=29$), and loss to follow up at 3 months ($n=194$). Overall, the exclusion criteria removed 399 ICH subjects, leaving 744 for this analysis. Baseline variables are presented in Table 1. Of the 289 subjects (39%) who received AED for prophylaxis, the vast majority (89%) received levetiracetam.

There were important racial/ethnic differences in patient characteristics (Supplemental Table I): white patients were older ($p=3.59\times 10^{-18}$), more commonly had lobar ICH ($p=8.05\times 10^{-6}$), and were more likely to be on warfarin prior to ICH ($p=1.32\times 10^{-5}$). Black patients had smaller hematoma volumes ($p=0.02$) and more frequent IVH ($p=0.04$). Craniotomy was more frequent in Hispanic patients ($p<0.001$).

Correlates of AED use

Baseline characteristics differed between subjects who received AED prophylaxis and those who did not (Table 2). AED use was markedly higher in lobar ICH subjects ($p=6.4\times 10^{-9}$) and in those with larger hematomas ($p=3.3\times 10^{-9}$). Craniotomy was more common in patients who received AED ($p=0.001$). AED recipients had lower GCS at admission ($p=0.03$), but the difference (12.2 vs. 12.6) is not clinically significant. In contrast, there were no differences in AED prophylaxis across age, sex, and race/ethnicity. Using stepwise logistic regression, only $\log_e$ hematoma volume ($p=1.4\times 10^{-5}$, OR=1.38, 95% CI=1.19–1.59) and lobar/non-lobar dichotomy ($p=2.8\times 10^{-5}$, OR=2.09, 95% CI=1.48–2.95) were significantly associated with AED prophylaxis ($p<0.05$).

AED use as a predictor of outcomes

Several baseline variables were associated with poor outcome in unadjusted models (Supplemental Table II). In particular, lower admission GCS strongly predicted poor 3 month outcome (OR=0.75, $p=1.0\times 10^{-24}$). Older age (5-year OR=1.26, $p=5.5\times 10^{-6}$) and female sex (OR=1.58, $p=0.002$) were also associated with poor outcome. Larger hematoma volume ($\log_e$ volume OR=2.37, $p=2.5\times 10^{-25}$), presence of IVH (OR=3.81, $p=1.0\times 10^{-18}$), craniotomy (OR=3.08, $p<0.001$), and prophylactic AED use (OR=1.40, $p=0.03$), were each associated with worse outcome at three months. We found no differences in three-month outcome among the three ethnicities ($p=0.30$), or with regard to p. After adjusting for GCS, age, race/ethnicity, sex, $\log_e$ -transformed hematoma volume, presence of IVH, and craniotomy, prophylactic AED use was no longer associated with 3 month outcome (Table 3, OR=1.11, $p=0.62$). In fact, the univariate association for prophylactic AED use ($p=0.03$, Supplemental Table II) was no longer significant in simpler models that controlled only for ICH volume (OR=0.95, $p=0.78$, 95% CI=0.68–1.33) or GCS at admission (OR=1.31, $p=0.11$, 95% CI=0.94–1.82). In the full model, age, sex, increasing hematoma volume, lobar ICH, presence of IVH, and low GCS at admission remained significant predictors of poor outcome at 3 months.

Discussion

Our analysis of a large prospective observational ICH study does not support the hypothesis that AED prophylaxis, predominantly with the use of levetiracetam, is independently associated with poor outcome at three months. Despite recent American Heart Association/American Stroke Association guidelines,⁸ our observations suggest that AED prophylaxis following ICH is common. Our finding that AED use was no longer associated with poor outcome in univariate analysis after controlling for hematoma volume or admission GCS provides indirect evidence that patients with more severe ICH may preferentially receive AED prophylaxis. In Battey et al., when the cohort was restricted to patients surviving through day 5, any association between AED exposure and poor outcome disappeared.⁹ This also raises the possibility of confounding by indication, and makes adjustment for factors associated with poor outcome in ICH essential.⁹ Predictors of poor outcome in this analysis—advanced age, increasing hematoma volume, and low admission GCS—mirror other studies.¹⁰

In prior reports examining the association of AED prophylaxis with poor outcome, phenytoin was the predominant medication prescribed^{3,4,11}. Fever and adverse cognitive effects were commonly observed³ and may mediate the relationship between phenytoin and poor outcome.¹² Our study—the largest of its kind to date—is powered to detect effect sizes one seventh of those previously reported.^{3, 4} Another report also found no association between levetiracetam use and poor outcome, although the number of subjects was small and short-term seizure recurrence was the endpoint.¹¹ Levetiracetam has been associated with improved outcome in a small observational analysis of ICH.¹³ In contrast to earlier reports in which phenytoin was the predominant AED used, use of levetiracetam does not appear to be associated with poor outcome.

There are potential limitations of this analysis. First, because of the high mortality of ICH, there is the possibility of survival bias. The ERICH methodology reduces this bias by employing a “hot pursuit” method whereby sites screen and enroll patients within 48 hours of admission. Secondly, we did not employ cEEG; future studies examining the role of AED use may focus on identification of subclinical seizures. Evidence from this study indicates that any adverse effect of AED use on outcome is likely small and of little clinical impact, although the role of AED would best be confirmed by a randomized controlled trial. Finally, patients lost to follow up are a limitation to this analysis, though their ICH severity (volume, initial GCS) and frequency of AED use was less common.

In conclusion, we found that prophylactic AED use, predominantly with the use of levetiracetam, is not associated with poor outcome in ICH after adjusting for hematoma volume or GCS at admission. Our data suggest that AEDs are used by experienced vascular neurologists and neurocritical care specialists in about 40% of patients with ICH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Clinical Characteristics (n=744)

Patient characteristics	n (%)
Age in years (mean $\pm$ SD)	60.5 $\pm$ 14.6
Female	307 (41.3%)
Race/Ethnicity	
White non-Hispanic	182 (24.5%)
Black non-Hispanic	307 (41.3%)
Hispanic	255 (34.3%)
ICH Location	
Lobar	207 (27.8%)
Non-Lobar	
Deep (includes 11 primary IVH)	446 (59.9%)
Cerebellum	55 (7.4%)
Brainstem	36 (4.8%)
Admission GCS, mean $\pm$ SD	12.4 $\pm$ 3.7
median (IQR)	15 (11–15)
Hematoma Volume (cc), mean $\pm$ SD	20.64 $\pm$ 24.95
range	0–152.96
median (IQR)	11.46 (4.11–27.11)
Presence of Intraventricular Hemorrhage	337 (45.3%)
Craniotomy	56 (7.5%)
Warfarin during 2 weeks prior to onset of ICH	67 (9.0%)
AED prophylaxis during hospital stay	289 (38.8%)
AED medications, N (% of 289)	
levetiracetam	248 (85.8%)
phenytoin/fosphenytoin	31 (10.7%)
levetiracetam & phenytoin	10 (3.5%)

Table 2

Patient characteristics associated with AED prophylaxis.

Variable	AED prophylaxis (n=289)	No AED prophylaxis (n=455)	p
Age, mean $\pm$ SD (median)	60.8 $\pm$ 15.3 (59)	60.4 $\pm$ 14.1 (58)	0.79
Female	121 (41.9%)	186 (40.9%)	0.79
Race/Ethnicity			0.11
White non-Hispanic	82 (28.4%)	100 (22.0%)	
Black non-Hispanic	117 (40.5%)	190 (41.8%)	
Hispanic	90 (31.1%)	165 (36.3%)	
Lobar ICH	115 (39.8%)	92 (20.2%)	<0.001
Admission GCS, mean $\pm$ SD (median)	12.2 $\pm$ 3.8 (14)	12.6 $\pm$ 3.7 (15)	0.03
Hematoma volume (cc), mean $\pm$ SD (median)	25.8 $\pm$ 26.3 (16.8)	17.4 $\pm$ 23.5 (9.2)	<0.001
Intraventricular Hemorrhage	140 (48.4%)	197 (43.3%)	0.17
Craniotomy	33 (11.4%)	23 (5.1%)	0.001
Warfarin before ICH	26 (9.0%)	41 (9.0%)	0.99

P-values for differences between groups are based on the nonparametric Wilcoxon rank sums test for continuous variables and contingency table chi square statistics for categorical variables.

Table 3Multivariable predictors of poor 3 month outcome (mRS ≥ 4 vs. mRS <4)

Predictor Variables	Odds Ratio	95% Confidence Interval	p ^I
AED use	1.11	0.74–1.65	0.61
Ethnicity			0.65
Hispanic	1.17	0.70–1.95	
Non-Hispanic Black	1.19	0.71–2.00	
Female	1.60	1.08–2.36	0.02
Age	1.07	1.05–1.08	<0.001
Hematoma Volume ^I	2.39	1.94–2.95	<0.001
Lobar	0.31	0.19–0.51	<0.001
IVH Presence	2.17	1.46–3.22	<0.001
Admission GCS	0.81	0.76–0.87	<0.001

^I P-value, odds ratio (OR) and 95% confidence interval (CI) are from the multivariate logistic regression model. ICH volume is modeled as natural log(volume+1), with the OR corresponding to a change of one on the log scale. The OR for age of onset is for a change of 5.