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Seizures and antiepileptic drugs in patients with spontaneous intracerebral hemorrhages

Shraddha Srinivasan [a], Haewon Shin [b], Sherry H.-Y. Chou [c], Page B. Pennell [d], Barbara A. Dworetzky [d], Jong Woo Lee [d,*]

[a] The Neurological Institute of New York, Columbia University Medical Center, New York, NY 10032, United States
[b] Department of Neurology, University of North Carolina, 2119 Physician's Office Building, 170 Manning Drive, Chapel Hill, NC 27599, United States
[c] Division of Stroke and Critical Care Neurology, Department of Neurology, Brigham and Women's Hospital/Harvard Medical School, Boston, MA 02115, United States
[d] The Edward B Bromfield Comprehensive Epilepsy Program, Department of Neurology, Brigham and Women's Hospital/Harvard Medical School, Boston, MA 02115, United States

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ABSTRACT

Purpose: Patients with intracerebral hemorrhage (ICH) are often initiated on antiepileptic drugs without a clear indication. We compared the percentage of patients with spontaneous ICH who had seizures at onset or during hospitalization, and examined empiric use of antiepileptic drugs (AEDs) in these patients in 2 cohorts 10 years apart.
Methods: Using a clinical data registry at a tertiary care adult hospital, we retrospectively selected admissions for spontaneous ICH between 1/1/99–12/31/00 (Cohort A, $n = 30$) and 1/1/09–12/31/10 (Cohort B, $n = 108$). Clinical, neurophysiological and radiological data were collected in both cohorts.
Results: In Cohorts A and B respectively, AEDs were started in 53.3% and 50.0%, and continued on discharge in 50.0% and 20.4% of patients; 86.6% and 59.1% of patients discharged on AEDs did not have a clinical/electrographic seizure or epileptiform EEG findings. Seizures occurred in 6.6% and 13.0% in Cohorts A and B respectively. The presence of a seizure at presentation ($p = 0.01$) and during hospitalization ($p = 0.02$) were predictors for continuing AED on discharge.
Conclusion: In both cohorts, a significant number of patients were discharged on AEDs without a clear indication, though there is a change in practice between the two cohorts.

1. Introduction

Seizures are an important neurological complication of spontaneous intracerebral hemorrhage (ICH). In a large clinical series of 761 consecutive patients, early seizures occurred in 4.2% of patients, and 8.1% had seizures within 30 days of ICH onset.[1] They may be difficult to detect because they are often non-convulsive in nature.[2,3] ICH-related seizures may be associated with adverse outcomes. However, in another population based study, the presence of seizures in ICH was not found to be an independent predictor of poor neurological outcome.[4] The latest AHA/ASA guidelines for management of spontaneous ICH state that only patients with clinical seizures and those with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs (AEDs).[5]

Nonetheless, the use of AEDs presents a difficult management decision. Patients who are admitted to the neurological intensive care unit (ICU) with spontaneous intracerebral hemorrhage are frequently loaded with or started on AEDs in the emergency department. Although there may be no clear indication for AED therapy, a significant proportion of patients may nevertheless be discharged on it. Use of AEDs may be independently associated with poor outcome in patients with intracerebral hemorrhage[6,7] and subarachnoid hemorrhage.[8–10] Furthermore, AEDs have not been demonstrated to prevent epileptogenesis.[11,12] Thus, in the absence of clinical or electrographic seizures, there is insufficient evidence to support the early use of antiepileptic drugs in patients with spontaneous parenchymal and intraventricular hemorrhages.[5]

A better understanding of the risk factors of seizures following intracerebral hemorrhages is needed to predict which patients will require treatment. In this study, two cohorts 10 years apart were examined to evaluate changing trends in management, especially in the setting of recent increased use of EEG monitoring in such patients. Using these two cohorts, we sought to compare the percentage of patients with spontaneous ICH, who experienced clinical or electrographic seizures at onset or during hospitalization, the percentage of patients who were started on an AED, and the percentage of patients discharged on an AED in the absence of a clinical or electrographic seizure.

* Corresponding author. Tel.: +617 732 7547.
E-mail address: jlee38@partners.org (J.W. Lee).

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2. Methods

2.1. Patient selection

Using a clinical data registry (Research Patient Data Registry or RPDR)[13] at a tertiary care adult hospital, we retrospectively selected all admissions for spontaneous intracerebral hemorrhages between 1/1/99–12/31/00 (Cohort A), and 1/1/09–12/31/10 (Cohort B), as identified by their ICD-9 code. Inclusion criteria were: greater than or equal to 18 years of age with supratentorial ICH confirmed on head CT. Patients with vascular malformations including cavernomas, AVMs and aneurysms, traumatic brain injury (TBI), primary subarachnoid and subdural hemorrhages, infratentorial hemorrhages, hemorrhagic infarcts, hemorrhagic intracranial primary or secondary malignancies, and patients with a prior history of epilepsy, were excluded retrospectively by chart review. The RPDR search criteria were deliberately nonspecific so as to minimize the chances of inadvertently excluding eligible patients. As a result, the search was also expected to capture a large number of ineligible patients, such as those whose presenting neurological dysfunction was not primarily ICH despite a small ICH component, or patients who were primarily treated at other institutions but who had a subsequent potentially unrelated admission at our institution. Patients whose goals of care were changed to ''comfort measures only'' (CMO) within 5 days of presentation, or those who did not survive beyond 5 days of hospitalization, were analyzed separately to prevent confounding since the decision to prophylactically start AEDs may have been affected by their CMO status and a rational decision to discontinue AEDs on discharge would not have been made. This study was approved by the Institutional Review Board.

2.2. Clinical/laboratory variables

The following clinical data were analyzed in both cohorts: demographics including age and sex, date of admission, seizure history and neurosurgical intervention. The presence of any clinical and/or electrographic seizures at presentation, or at any time prior to discharge, was obtained. We also recorded the use of antiepileptic drugs during hospitalization and at the time of discharge.

The subjects were classified according to hemorrhage location into cortical, deep and primary intraventricular. The presence of any associated subdural, subarachnoid and intraventricular extension of the hemorrhage was documented. The hemorrhage volume was calculated by the ABC/2 formula on the admission and subsequent CT scans.[14] The presence of hematoma expansion and increase in midline shift were documented as per the radiologist's report.

Continuous and routine EEGs were recorded digitally using 21 standard scalp electrodes placed according to the international 10–20 system. We recorded the presence of clinical and electrographic seizures, interictal epileptiform discharges (spikes, sharp waves), including periodic epileptiform patterns such as lateralized periodic discharges and generalized periodic epileptiform discharges.

2.3. Statistical analysis

Categorical variables were compared using chi-square and Fisher's exact test. Continuous variables were compared using Student's *t*-test or Wilcoxon rank-sum test depending on data normality. Logistic regression was used to determine patient characteristics influencing AED initiation on admission, and AED on discharge. These included seizures at presentation, seizures during hospitalization, age, sex, location of the hemorrhage in the temporal region, hematoma expansion and presence of neurosurgical intervention. Data were analyzed with the statistical software SAS version 9.2 (SAS Institute, Cary, NC).

3. Results

3.1. Study cohorts

From January 1999 to December 2000, a total of 199 patients were admitted with the diagnosis of intracerebral hemorrhage. After applying the inclusion and exclusion criteria mentioned above, we excluded 169 patients, and 30 patients were included in our study (Cohort A). The most common reasons for excluding the remaining patients were the presence of vascular malformations on subsequent CT Angiograms, significant TBI, infratentorial hemorrhages and patients admitted to our partner institution (Massachusetts General Hospital). Between January 2009 and December 2010, 521 patients with the diagnosis of intracerebral hemorrhage were admitted. A total of 108 patients were included in the study (Cohort B). The demographic characteristics of these two cohorts are described in Table 1. The reasons for excluding the remainder of the patients were similar to Cohort A. Table 2 summarizes the characteristics of excluded patients in both cohorts.

3.2. EEGs

In Cohort A, only 2 patients (6.7%) underwent routine EEGs and no patients underwent continuous EEG monitoring. In Cohort B, 47 (43.5%) patients underwent EEG studies, of which 30 patients had continuous EEG monitoring over 24 h or more, and 17 patients had routine EEGs. One patient in Cohort A (3.3%) and 8 patients in Cohort B (7.4%) were found to have epileptiform activity on the EEGs. The patient in Cohort A had sharp waves. Of the 8 patients in Cohort B, 4 had electrographic seizures, 2 had periodic epileptiform discharges and 2 had epileptiform discharges that were not periodic.

3.3. Seizures

Seizures occurred in 6.7% ($n = 2$) and 13.0% ($n = 14$) of patients in Cohorts A and B, respectively (Table 3). In Cohort A, 6.7% ($n = 2$)

Table 1
Demographics.

Characteristics	1999–2000 Cohort A	2009–2010 Cohort B	*P* value
Age (mean ± SD)	75.13 ± 11.47	73 ± 13.48	0.82
Women	17 (56.7%)	48 (44.4%)	0.48
Deceased	1 (3%)	17 (16%)	0.12
ICH location			
Cortical	20 (66.7%)	45 (41.7%)	0.03
Deep	10 (33.3%)	55 (50.9%)	
IVH	0 (0%)	8 (7.4%)	
ICH volume			
<50 cc	5 (16.7%)	80 (74.1%)	0.18
≥50 cc	3 (10.0%)	17 (15.8%)	
Difficult to assess/not available	22 (73.3%)	11 (10.2%)	
Mean (SD)	Not available	27.5 (29.6)	
Presence of SAH	4 (13.3%)	32 (29.6%)	0.10
Presence of SDH	3 (10.0%)	14 (13.0%)	1.00
Hematoma expansion	3 (10.0%)	19 (17.6%)	0.41
Neurosurgical intervention	10 (33.3%)	27 (25.0%)	0.36
Total patients	30	108	

ICH: intracerebral hemorrhage, IVH: intraventricular hemorrhage, SAH: subarachnoid hemorrhage, SDH: subdural hemorrhage, INR: international normalized ratio, SD: standard deviation, and cc: cubic centimeters.

Table 2
Excluded patients.

Exclusion criteria	1999–2000 Cohort A	2009–2010 Cohort B	*P* value
Vascular malformations	21	32	0.08
Infratentorial hemorrhage	23	26	0.01
Early CMO	11	28	1.00
TBI	21	97	0.01
Insufficient data	8	8	0.09
No ICH	7	25	0.42
Hemorrhagic infarct	14	16	0.04
Tumor	12	27	0.86
Received care at another institution	24	63	0.80
Primary SAH/SDH	28	88	0.21
History of epilepsy/AEDs prior to presentation	0	1	1.00
Venous sinus thrombosis	0	3	0.56
Total patients excluded	169	413	

TBI: traumatic brain injury, CMO: comfort measures only, ICH: intracerebral hemorrhages, and SAH/SDH: subarachnoid hemorrhage/subdural hemorrhage.

patients had clinical seizures either on presentation or during admission. No electrographic seizures were recorded in the 2 patients who underwent routine EEGs. In Cohort B, 9.2% patients ($n = 10$) had clinical seizures on presentation and 3.7% ($n = 4$) patients had clinical and electrographic seizures during hospital stay. Of the 42.5% ($n = 46$) patients in Cohort B who had either continuous or routine EEGs, only 0.9% ($n = 1$) patients had subclinical electrographic seizures.

3.4. AEDs

In Cohort A, 53.3% ($n = 16$) patients were started on or loaded with an AED at some point during hospitalization, and 50.0% ($n = 15$) were discharged on an AED. In Cohort B, 50.0% ($n = 54$) patients were started on an AED, and 20.4% ($n = 22$) were discharged on an AED ($p = 0.002$). Of the patients in Cohort A who were discharged on an AED, 86.6% did not have a clinical or electrographic seizure at any point of time between presentation and discharge, nor did they have any epileptiform findings on their EEGs. Similarly, of the patients who were discharged on an AED in Cohort B, 59.1% did not have a clinical/electrographic seizure or epileptiform EEG findings. Some of the reasons for the patients being discharged on an AED included the presence of 'sharp transients' on their EEGs, cortical location of the ICH, neurosurgical procedures and a 'possible clinical seizure' at presentation. Reasons were not documented for several patients. Of note, the percentage of temporal lobe hematomas was 16.6% ($n = 5$) and 7.4% ($n = 8$, $p = 0.16$) in Cohorts A and B respectively. Within this subpopulation, AEDs were started in 60% ($n = 3$) and 75% ($n = 6$, $p = 1.0$), and were continued on discharge in 60% ($n = 3$) and 37.5% ($n = 3$, $p = 0.59$) in Cohorts A and B respectively.

Characteristics of the patients who underwent neurosurgical intervention are outlined in Table 4. The percentage of patients who had undergone neurosurgery and were discharged on an AED was higher in Cohort A (80.0% vs 18.5%, $p = 0.001$).

In patients whose goals of care was changed to CMO within less than 5 days from presentation, 5 out of 11 (45.4%) patients from Cohort A and 9 out of 26 (34.6%) of patients from Cohort B were started on AEDs upon presentation ($p = 0.74$). None of the patients from either cohort presented with or developed clinical seizures during hospitalization. EEG studies were not obtained in most patients; only one patient in Cohort B received an EEG, which did not reveal any epileptiform discharges.

3.5. Radiological characteristics

The percentages of cortical and deep ICH were 66.7% ($n = 20$) and 33.3% ($n = 10$) in Cohort A, and 41.7% ($n = 46$) and 50.9% ($n = 55$) in Cohort B. Of all the patients with cortical hematomas ($n = 20$) in Cohort A, the percentages of patients with frontal, temporal, parietal and occipital hematomas accounted for 35.0% ($n = 7$), 25.0% ($n = 5$), 20.0% ($n = 4$) and 20.0% ($n = 4$) respectively. Similarly in Cohort B, the percentages were 28.2% ($n = 13$), 17.3% ($n = 8$), 30.4% ($n = 14$) and 23.9% ($n = 11$) respectively.

An overwhelming majority of patients who had seizures in both cohorts had cortical hemorrhages (Cohort A: 100% and Cohort B: 93.3%). In Cohort A, both patients who seized had stable serial scans. In Cohort B, of the 15 patients who had clinical or electrographic seizures, 3 patients had hematoma expansion on repeat CT scans. Hematoma expansion was determined as per documentation by the radiologist in the CT scan report.

3.6. Predictors of AED use

In Cohort A, there were no significant predictors of patients started or discharged on AEDs. In Cohort B, there were no significant predictors for starting an AED. However, the presence of a seizure at presentation ($p = 0.02$) and during hospitalization ($p = 0.04$) were found to be significant predictors for discharging a patient on an AED. Also in Cohort B, temporal location of the hemorrhage, ($p = 0.07$) showed a trend toward being a significant predictor for AEDs continued on discharge.

When both cohorts were combined together, the presence of a seizure during hospitalization ($p = 0.04$) and surgical intervention ($p = 0.03$) were both independent significant predictors for AED being started. On the other hand, the presence of a seizure at presentation ($p = 0.01$) and during hospitalization ($p = 0.02$) were independent significant predictors for continuing AED on discharge. When cohort membership was used as an independent variable, it was found to be a significant predictor ($p = 0.0003$) for AED continuation on discharge.

Table 3
Results.

Characteristics	1999–2000 Cohort A	2009–2010 Cohort B	*P* value
AED started	16 (53.3%)	54 (50.0%)	0.84
EEGs performed (routine + continuous)	2 (2 + 0) (6.7%)	47 (17 + 30) (43.5%)	0.0001
Clinical seizures on presentation/during admission	2 (6.6%)	14 (13.0%)	0.52
Electrographic seizures during admission	0 (0%)	4 (3.7%)	0.58
Epileptiform activity on EEG	1 (3.3%)	8 (7.4%)	0.68
Discharged on antiepileptic drugs	15 (50.0%)	22 (20.4%)	0.002
Location of hemorrhage in patients who had seizures	Cortical: 2 (100%), deep: 0	Cortical: 14 (93.3%), deep: 1 (6.7%)	1.00
Changes in serial CT scans in patients who had seizures	Stable: 2 (100%), hematoma expansion: 0 (0%)	Stable: 12 (80.0%), hematoma expansion: 3 (20.0%)	1.00

EEG: electroencephalogram, AEDs: antiepileptic drugs.

Table 4
Neurosurgical patients.

Characteristics	1999–2000 Cohort A	2009–2010 Cohort B	*P* value
Neurosurgical intervention[a]	10/30 (33.3%)	27/108 (25.0%)	0.36
Started on AEDs	9/10 (90.0%)	16/27 (59.3%)	0.12
Clinical or electrographic seizures on presentation/during admission	1/10 (10.0%)	1/27 (3.7%)	0.47
Discharged on AEDs	8/10 (80.0%)	5/27 (18.5%)	0.001

[a] Includes patients who underwent external ventricular drain placement or craniotomies.

4. Discussion

This is a retrospective study of 2 cohorts of 30 and 108 patients, with spontaneous intracerebral hemorrhage, in whom we studied the incidence of clinical and electrographic seizures, and the use AEDs during hospitalization and upon discharge. The frequency of seizures in our study is similar to other studies, which has ranged from 2.8% to 18% and as high as 19% in more recent studies which have involved continuous EEG monitoring in all of their patients.[15] In our study, seizures occurred at the rate of 6.7% and 13% in Cohorts A and B, respectively.

We found that a significant proportion of patients were being started on an AED in the absence of clearly identifying clinical indications in both cohorts. Our study demonstrates a change in practice in the management of hemorrhage-related seizures within a 10-year period. Although AEDs were initiated in patients at similar rates, significantly fewer patients were discharged on AEDs in Cohort B (2009–2010) as compared to Cohort A (1999–2000). This may be due to several reasons. The AHA guidelines published in 1999, state that prophylactic antiepileptic therapy in patients with ICH may be considered for a month and then tapered and discontinued if no seizures occurred during treatment.[16] This may have influenced the more frequent use of AEDs in Cohort A (January 1999–December 2000). The subsequent publication of the American Heart Association clinical guidelines for the management of spontaneous intracerebral hemorrhage in 2007, which recommended against prophylactic use of AEDs,[17] may have altered AED management practices more recently. There was also a marked increase in the use of EEGs in Cohort B, which also likely led to the discontinuation of AEDs in patients who may otherwise have been discharged on them. This change occurred despite the widespread introduction of less toxic modern AEDs, particularly levetiracetam, replacing phenytoin, during this time at our institution.[18]

The optimal use of AEDs in patients with intracerebral hemorrhages remains to be determined. ICH-related seizures are associated with higher NIHSS scores, increasing midline shift, and a trend toward poor outcome, although it is not clear whether there is a causative effect of seizures or whether seizures are merely markers of greater injury.[2,3] On the other hand, there are other prospective and population based studies that have shown that clinical seizures in ICH are not an independent predictor of poor neurological outcome or mortality.[4,19] In a recent clinical trial, prophylactic use of valproic acid in non-traumatic, non-aneurysmal spontaneous intracerebral hemorrhage was associated with a trend toward decreasing early seizures (<14 days post-event) as well as improved NIHSS scores at one year, though it did not reduce the incidence of later seizures.[12]

Frequent unwarranted use of AEDs can put patients at a high risk for adverse drug reactions, increased sedation, and unnecessary financial burden to the patient as well as healthcare in general. In a retrospective study of patients with ICH, prophylactic AED use (predominantly phenytoin) was associated with an independent poor outcome at 90 days.[6,7] Other studies have shown similar results in patients with subarachnoid hemorrhages.[8–10]

The retrospective nature of this study necessarily limits its interpretation. The size of the first cohort is markedly smaller than the second, which may be due to a number of reasons. The neuroscience ICU at our institution doubled in capacity in the last ten years, which was equal to the time gap between the 2 cohorts. In addition, the RPDR query may have found a greater number of patients in the more recent Cohort B due to a more widespread use of electronic medical records and more accurate coding as compared to Cohort A. However, the baseline characteristics between the two cohorts are similar, and there does not appear to be a selection bias. The two cohorts are similar in most aspects of demographics, except for the location of the hemorrhage. A larger percentage of cortical hemorrhages (66.6%) were noted in Cohort A, as compared to Cohort B (41.6%). No clear explanation for this was found. We also did not find a significant association between hematoma expansion and seizure frequency, possibly due to the relatively small number of patients who experienced seizures. Our cohorts most likely under represent the incidence of electrographic seizures in patients with spontaneous ICH, as the majority of patients in Cohort A, and more than 50% of patients in Cohort B did not undergo continuous EEG monitoring. This study was not designed with an aim to assess the outcomes of patients upon discharge and beyond, and it is therefore unclear whether the reduction in AED use conferred any clinical benefit.

The AHA guidelines[1] advising against prophylactic treatment with AEDs was introduced during 2010 as our data was being collected, possibly biasing the results of Cohort B. However, the guidelines were released in September 2010, and we do not expect that practice would have shifted. We have verified our data to ensure that the patients admitted after the publication of the article were not less likely to be started on AEDs; 9 out of 16 patients admitted after September 2010 were started on AEDs, including 7 out of 14 who did not present with seizures at onset. A further study comparing a 2 year cohort after 2010 is strongly warranted.

5. Conclusion

Nevertheless, our study has demonstrated further need for consistent management of seizures and AEDs in these patients. Therefore, a more rational approach, with greater early use of continuous EEG monitoring, may result in both overall reduction in AED use while appropriately treating patients with subclinical seizures. Further studies of such clinical protocols need to be investigated.

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