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Seizures and antiepileptic drugs in patients with spontaneous intracerebral hemorrhages

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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.

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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.

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