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The prophylactic use of an antiepileptic drug in intracerebral hemorrhage

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Abstract

Objective—Patients with intracerebral hemorrhage (ICH) are at increased risk for both early seizures and later epilepsy. There is a common, but unproven, practice of prescribing a prophylactic antiepileptic drug (PAED) to prevent seizures, but the safety and efficacy of this practice is unclear, as is the optimal drug for this purpose. The objective of the study is to evaluate whether patients presenting with acute, spontaneous intracerebral hemorrhage (ICH) benefit from prescription of prophylactic antiepileptic drug (PAED).

Method—All patients with a discharge diagnosis of acute, spontaneous ICH admitted to our institution in the calendar years 2004 and 2007 were included. We retrospectively reviewed the records for baseline characteristics, hospital course, PAED use, early seizures, length of stay, discharge disposition, and death.

Results—157 patients met our criteria for review. 46 (29%) patients were placed on a PAED. 12 (7.6%) had early seizures. 11% of patients placed on a PAED had an early seizure versus 6.3% who not placed on a PAED. Death or hospice discharge was less common in patients prescribed a PAED, while length of stay was longer, however neither of these differences were significant after adjustment for multiple comparisons.

Interpretations—Our study confirms previous reports that patients with acute, spontaneous ICH are at an increased risk for early seizures. PAED use in our series was not significantly associated with the risk of early seizures, long-term epilepsy, disability, or death.

Keywords

Intracerebral hemorrhage; Antiepileptic drugs; Epilepsy

1. Introduction

Acute, spontaneous intracerebral hemorrhage (ICH) is a common cause of disability and death, with an estimated annual incidence of 33 people per 100,000, and 5% dying before arrival at medical facilities [1]. For the majority that survive to hospital presentation, the overall prognosis remains grim, with 35% dying within 7 days and 50% by 30 days [1]. Because of the poor prognosis for the large number of ICH patients each year, any intervention that could reduce the risk of morbidity or mortality, even of modest efficacy, could have an important public health impact.

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Patients with ICH are also at increased risk for both early seizures and later development of epilepsy. The largest published series showed a 30-day risk of clinical seizures of 8.1%, while another series showed electrographic seizures in 28% of ICH patients within the first 72 h [2,3]. There is a common, but unproven, practice of prescribing a prophylactic antiepileptic drug (PAED) to prevent seizures, but the safety and efficacy of this practice is unclear. Even if early seizures were prevented with use of a PAED, it is not clear whether that benefit would outweigh the potential toxicity, or if there would be any effect on the long-term outcomes of epilepsy, disability, or death. Both phenytoin (PHT) and levetiracetam (LEV) are commonly used. To evaluate these issues, we performed a retrospective medical record review to evaluate whether prescription of PAED to patients presenting with acute, spontaneous ICH would be associated with a lower rate of early seizures.

2. Materials and methods

Patients age 18 and greater with a discharge diagnosis of ICH during the calendar years 2004 and 2007 were included. Their medical records were reviewed for baseline characteristics, hospital course, PAED usage, early seizures, length of stay, discharge disposition, and death. The study was approved by the University of Wisconsin Institutional Review Board.

Data recorded included age, sex, past medical history, pertinent medications, presumed etiology of the hemorrhage and its location, clinical severity at presentation (ICH score [4]), functional status through last recorded follow up, clinical and electrographic seizures (number, timing, type), procedures performed, length of stay, discharge disposition, prescriptions of a PAED, and associated adverse reactions.

Our primary outcome was whether prescription of PAED to patients presenting with acute, spontaneous ICH would be associated with a lower rate of early seizures. Our secondary outcomes were if PAED prescription for ICH patients would be associated with lower rates of long-term epilepsy, disability, or death, and if there appeared to be a difference in these outcomes or adverse event rates between ICH patients prescribed PHT versus LEV.

Early seizures were defined as those occurring within 7 days of onset of ICH symptoms. Fisher's exact test was used for to assess for significance of all associations at a significance level of 0.05; significant differences were then adjusted for multiple comparisons including gender, premorbid epilepsy, location of hemorrhage and ICH score.

3. Results

162 patients had a discharge diagnosis of ICH during the examined time period, with 157 patients meeting our inclusion criteria, and their baseline data is shown in Table 1. None of the patients with premorbid epilepsy experienced an early seizure.

46 (29%) were placed on a PAED (15 on LEV, 26 on PHT). 5 patients were taking an AED at the time of their ICH, including gabapentin, carbamazepine, oxcarbazepine, LEV, or PHT. These subjects were included with the PAED group.

12 (7.6%) patients had early seizures, of which 5 (42%) were on a PAED. 11% of patients prescribed a PAED had an early seizure, while only 6.3% of patients not placed on an PAED had an early seizure (Table 2), which was not significantly different ($p = 0.34$). The number, timing and type of seizures were not determinable from the chart review.

Death or hospice discharge was less common in patients prescribed a PAED (24% versus 46%, $p = 0.02$), but this difference was no longer significant after adjustment for multiple comparisons (Table 3).

Length of stay was longer in patients prescribed a PAED (19.1 versus 9.18 days, $p = 0.006$), but this difference was also not significant after adjustment for multiple comparisons (Table 4).

84 patients had a lobar location of their ICH, of whom 35 were prescribed a PAED; 4 of whom had early seizures (11.4%). Of the 49 not prescribed a PAED, 5 had seizures (10.2%), which was not significantly different (Table 5).

Of patients prescribed PHT as a PAED, 5 had possible associated adverse reactions including fever and cough, Steven's Johnson syndrome, renal failure, hypotension and fever with elevated liver function tests (1 each). One patient prescribed LEV as a PAED developed thrombocytopenia which may have been associated with the medication. No other possible PAED-associated toxicities were identified.

4. Discussion

With this study we were not able to identify an association between the prescription of PAED to patients with acute, spontaneous ICH and adverse outcomes in general, or early seizures in particular. Death or hospice discharge was less common in patients prescribed a PAED, while length of stay was longer, however neither of these differences was significant after adjustment for multiple comparisons.

The practice of prescribing PAED to patients with acute, spontaneous ICH may not be beneficial in our population, or a modest benefit may be negated by toxicity of the drugs; alternatively several sources of bias in our study could have obscured the true effect of the intervention. This could be due to several factors which were not controlled in this study, such as other medical interventions, initial timing or dosing of the PAED, or other medical comorbidities. While we were able to obtain most of the known baseline confounding factors, as with any retrospective review there are limitations in the data available, and unknown factors could have affected the outcome. The small number of cases may also have obscured a true difference. Several recent studies have suggested that PAED use in general, and PHT specifically, has been associated with worse outcomes for patients with acute, spontaneous ICH [5,6].

5. Conclusion

In summary, we did not find a difference in the outcomes of interest between ICH patients prescribed an PAED versus those that were not. Randomized, controlled trials of this common, but unproven, practice are needed, perhaps allocating patients to placebo, PHT, and LEV arms. Additional study would also be helpful of larger groups of patients to identify subgroups with differential benefit to this practice. This study and other recent studies do not currently support the practice of prescribing PAED to patients with acute, spontaneous ICH.

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Table 1

Baseline data.

	PAED	No PAED
Number of patients	46	111
Mean age	60	64
Female	30%	34%
Premorbid epilepsy	7	1
Mean ICH score	1.39	1.78
		ICHscore
0	9 (20%)	25 (23%)
1	23 (50%)	28 (25%)
2	6 (13%)	21 (19%)
3	3 (7%)	22 (20%)
4	5 (11%)	13 (12%)
5	0 (0%)	2 (2%)
6	0 (0%)	0 (0%)

Table 2

Early seizures by PAED status.

	No early seizures	Early seizures
No PAED	104	7 (6.3%)
PAED	41	5 (11%)
Overall	145	12 (7.6%)

Table 3

Disposition by PAED status.

	Disposition			
	Home	**Inpatient rehabilitation**	**Skilled nursing facility**	**Hospice or death**
No PAED	23 (21%)	20 (18%)	16 (15%)	50 (46%)
PAED	11 (24%)	13 (28%)	11 (24%)	11 (24%)

Table 4

Length of stay by PAED status.

Length of stay	No PAED	PAED
0–7 days	71 (64%)	17 (37%)
8–14 days	20 (18%)	10 (22%)
15–21 days	13 (12%)	10 (22%)
More than 22 days	7 (6%)	9 (20%)

Table 5

Disposition by initial ICH score.

	0	1	2	3	4	5
Hospice or death	2 (6%)	9 (25%)	15 (56%)	18 (72%)	15 (88%)	2 (100%)
SNF	3	9	10	4	2	0
Inpatient rehabilitation	12	9	2	2	0	0
Home	16	9	0	1	0	0
Total	33	36	27	25	17	2