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Survey of Prophylactic Antiseizure Drug Use for Nontraumatic Intracerebral Hemorrhage

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Abstract

Objective—Prophylactic antiseizure drugs (PAD) are commonly prescribed for nontraumatic intracerebral hemorrhage (ICH) despite limited evidence for this indication. We sought to determine the current prescribing patterns of the use of a PAD for ICH.

Methods—A 36-item survey was distributed to physicians that manage ICH patients soliciting details of PAD prescription in their practice.

Results—A total of 199 physicians responded to the survey, all of who manage between one and 50 or more ICH patients per year. The respondents were neurologists (32%), neurosurgeons (11%), and intensivists (57%) in academia (69%) and private practice (31%). PAD prescriptions were used: never (33%), 1–33% (35%), 34–66% (14%), 67–99% (9%) of the time, or always (9%). Most respondents performed electroencephalographic and serum level monitoring in at least some patients. Levetiracetam was used most often (60%), followed by fos/phenytoin (37%), for a usual duration of days (36%), weeks (47%), or months (17%). PAD prescription varied by patient characteristics and physician specialty. Perception of physician community consensus regarding PAD use for ICH among respondents ranged from strongly (7%) or weakly (23%) against the practice, to a fairly equal division of opinion (41%), to weakly (27%) or strongly (4%) in favor of the practice.

Conclusions—We found variability of multiple aspects of the current prescribing patterns and opinions regarding the use of a PAD for ICH. This variability is likely secondary to insufficient data. Clinical equipoise exists for this issue, and controlled trials would be both justified and useful.

Keywords

survey; prophylactic; prevention; antiseizure drug; antiepileptic drug; anticonvulsant; seizure; epilepsy; stroke; intracerebral hemorrhage

Introduction

The risk of early seizures and late epilepsy is increased after nontraumatic intracerebral hemorrhage (ICH).¹ There is an association of seizures after ICH and early complications, although it is unclear if the early seizures themselves cause early complications or long-term epilepsy, disability, or death.^{2–5} Early seizures after ICH could potentially lead to hemorrhage expansion due to elevated blood pressure, loss of stressed peri-hematoma neurons from increased metabolic demand, or epilepsy by strengthening aberrant neuronal networks.^{2–4} For these reasons, a prophylactic antiseizure drug (PAD) is often prescribed for ICH, despite limited evidence to support the safety or efficacy of this practice.⁶ The

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proposed benefits of this practice could possibly include reduced rates of early seizures, epilepsy, disability, or death.⁷ Risks may include allergic reactions, organ and bone marrow toxicity, or diminished recovery via antagonism of restorative neuroplasticity that requires normal synaptic activity.^{8,9} We sought to determine current patterns of PAD prescription for ICH by neurologists, neurosurgeons, and intensivists, and assess for equipoise for this practice for the purpose of assessing the need for further research.

Methods

A 36-item survey, with all questions required for submission, was emailed to stroke center directors and the 1,000 members of the Neurocritical Care Society soliciting details of PAD prescription for ICH in their practice, as well as their opinions about equipoise. The email encouraged recipients to forward it to applicable clinicians and responses were collected anonymously, so we were unable to know how many people viewed the email or the full survey without participating. Responses were compared to respondent characteristics using Fisher's exact test for categorical data or the Wilcoxon rank sum test for ordinal data, and p-values of < 0.05 were considered significant after Holm adjustment for multiple comparisons.

Results

The survey was completed by 199 physicians, for a response rate of probably less than 20%. Of respondents, 69% chose their position as primarily academic, while 31% chose private practice. The respondents described the majority of their practice as general neurology (16%), vascular neurology (17%), general neurosurgery (8%), vascular neurosurgery (3%), general critical care (12%), and neurocritical care (45%). When asked how many years prior they finished training, the respondents chose that they were currently in residency or fellowship (7%), 0 to 4 years (26%), 5 to 9 years (20%), 10 to 14 years (18%), 15 to 19 years (13%), and 20 or more years (17%). When asked, on average, how many patients they manage each year with ICH, the respondents chose 1 to 4 (5%), 5 to 9 (9%), 10 to 14 (8%), 15 to 19 (9%), 20 to 29 (12%), 30 to 39 (12%), 40 to 49 (9%), and 50 or more (38%).

The respondents prescribed a PAD for ICH patients: never (33%), 1–33% of the time (35%), 34–66% of the time (14%), 67–99% of the time (9%), or always (9%). Most respondents performed electroencephalographic monitoring and monitoring of PAD serum levels in at least some patients (Table 1). A PAD was prescribed for a usual duration of days (36%), weeks (47%), or months (17%). The PAD most often used was levetiracetam (60%), followed by fosphenytoin or phenytoin (37%), valproate (2%), lamotrigine (1%), and phenobarbital (1%).

There were no significant differences in responses between the physician subspecialties of general neurology, vascular neurology, general neurosurgery, vascular neurosurgery, general critical care, and neurocritical care, but the numbers were small with this many categories. After collapsing the specialties into neurology, neurosurgery, and critical care, we found that neurologists prescribed a PAD for ICH patients significantly less often than critical care physicians ($p=0.009$) and neurosurgeons ($p=0.016$). When neurologists did prescribe a PAD for ICH patients, however, they did so for significantly longer durations than critical care physicians ($p<0.001$) and neurosurgeons ($p=0.01$). While only 6% of the critical care physicians and 5% of the neurosurgeons reported prescribing a PAD for an average duration of months, 22% of the neurologists did.

There were no significant differences in responses between academic and private practice physicians, with different levels of years of experience (currently in training, 0–4, 5–9, 10–

14, 15–19, and 20 or more years after training), or with different numbers of ICH patients managed annually (1–4, 5–9, 10–14, 15–19, 20–29, 30–39, 40–49, and 50 or more).

PAD use differed based on ICH clinical and imaging characteristics (Table 1). The frequency of PAD prescription varied by combinations of ICH size (large versus small), hemispheric location (superficial versus deep), and arousal status (stuporous or comatose versus awake or drowsy). ICH location was the primary determinant of PAD prescription, with a higher frequency of prescription for superficial compared to deep hemispheric ICH ($p < 0.001$).

When asked if all else was equal, respondents stated that they were less likely to prescribe a PAD for intratentorial ICH ($p < 0.001$) and more likely to prescribe a PAD for patients with a history of seizures prior to their ICH ($p < 0.001$) when compared to other features that included: intraventricular extension, ventriculostomy placement, craniotomy with or without decompression, family history of epilepsy, heavy alcohol consumption, and age 80 or greater (Table 1).

When asked how effective a PAD for ICH would have to be to change the respondent's current practice, a much larger effect size was required if the only benefit was the prevention of early seizures when compared to later epilepsy, disability, or death ($p < 0.001$). If the only benefit was the prevention of early seizures, more respondents required a small number needed to treat of 2–4 (corresponding to a large effect size of an absolute risk reduction of 25 to 50%) compared to larger numbers needed to treat (5–9, 10–19, 20–39, and 40 or more). If the practice was shown to be effective against later epilepsy, disability, or death, more respondents would accept a large number needed to treat of 40 or more (corresponding to a small effect size of an absolute risk reduction of 2.5% or less) than any of the choices that involved a larger effect size (Table 1).

To assess equipoise, respondents were asked their perception of the consensus among the physician community regarding PAD use for ICH, which ranged from: strongly (7%) or weakly (23%) against the practice; to a fairly equal division of opinion (41%); to weakly (27%) or strongly (4%) in favor of the practice.

Conclusions

This survey provides an assessment of the current prescribing patterns and opinions regarding the use of a PAD after ICH, highlighting the existing variability of many aspects of the practice, despite guideline recommendations against it.⁶ We speculate that this variability is likely secondary to insufficient data available to assist clinicians with these decisions.¹

Our study has limitations. Some of the differences we found could be explained by factors that were not explored with the survey. For example, the finding that neurologists tended to prescribe a PAD for ICH less often but for a longer duration could reflect a difference in opinion about the optimal duration of PAD use between the specialties, or this could be due to differences in the severity of cases or duration of physician contact with ICH patients as they transition from the intensive care unit to the general ward to outpatient care. With our response rate, it is unclear if the respondents differed in an unexpected way from nonrespondents, and if the responses accurately reflect the clinician community of interest.

To our knowledge, this is the first survey of PAD use for ICH. This information may be useful for clinicians managing ICH patients, and investigators interested in pursuing studies exploring ways to reduce the risks and complications of early seizures and later epilepsy after ICH. Clinical equipoise appears to exist for this practice, and prospective controlled

trials would be both justified and useful. A possible reason for the limited evidence for this question to date may be the difficulties that were encountered in obtaining both quantity and quality of data over multiple trials of PAD use for traumatic brain injury.^{10,11} With such limited treatment options to improve outcomes for patients with ICH, however, we feel that the effort would be justified if there might be even a small potential benefit.

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Table 1

Percent of respondents choosing each answer.

On average, when you manage an ICH patient that has not had any clinical seizure-like events, how OFTEN do you:					
	Never	1-33%	34-66%	67-99%	Always
Prescribe prophylactic anticonvulsants?	33	35	14	9	9
Monitor serum levels of prophylactic anticonvulsants for dose adjustment?	37	25	10	9	20
Perform periodic EEG monitoring (such as an occasional or daily 1-2 hour recording)?	34	41	15	7	3
Perform continuous EEG monitoring (24 hours per day)?	44	41	11	3	2

On average, when you manage an ICH patient that has not had any clinical seizure-like events, for what DURATION do you:				
	Days	Weeks	Months	
Prescribe prophylactic anticonvulsants?	36	47	17	
Monitor serum levels of prophylactic anticonvulsants for dose adjustment?	48	36	16	
Perform periodic EEG monitoring (such as an occasional or daily 1-2 hour recording)?	78	15	7	
Perform continuous EEG monitoring (24 hours per day)?	95	3	1	

On average, how often would you prescribe prophylactic anticonvulsants for these types of ICH patients, when the hemorrhage is located in the cerebral hemispheres? DEFINITIONS: Large ICH = 30 ml or more, small ICH = less than 30 ml. Superficial ICH = near the cortex, deep ICH = near the basal ganglia. Stupor or coma = Glasgow Coma Scale (GCS) of 8 or less, awake or drowsy = GCS greater than 8.					
	Never	1-33%	34-66%	67-99%	Always
A large, superficial ICH in a stuporous or comatose patient	23	19	11	16	32
A large, superficial ICH in an awake or drowsy patient	30	19	10	18	24
A large, deep ICH in a stuporous or comatose patient	51	25	9	5	11
A large, deep ICH in an awake or drowsy patient	56	25	6	4	9
A small, superficial ICH in a stuporous or comatose patient	29	24	9	17	21
A small, superficial ICH in an awake or drowsy patient	38	24	11	14	14
A small, deep ICH in a stuporous or comatose patient	61	20	7	3	10

On average, how often would you prescribe prophylactic anticonvulsants for these types of ICH patients, when the hemorrhage is located in the cerebral hemispheres? DEFINITIONS: Large ICH = 30 ml or more, small ICH = less than 30 ml. Superficial ICH = near the cortex, deep ICH = near the basal ganglia. Stupor or coma = Glasgow Coma Scale (GCS) of 8 or less, awake or drowsy = GCS greater than 8.				
Never	1-33%	34-66%	67-99%	Always
72	15	6	2	5
A small, deep ICH in an awake or drowsy patient				

All else being equal, would you be more or less likely to prescribe prophylactic anticonvulsants to ICH patients with these features?				
MUCH LESS likely to prescribe	SOMEWHAT LESS likely to prescribe	This would not influence my decision	SOMEWHAT MORE likely to prescribe	MUCH MORE likely to prescribe
70	6	18	5	2
21	12	43	21	4
19	6	48	23	5
11	4	32	38	17
9	6	26	37	26
1	2	7	18	73
9	2	64	17	9
8	3	50	27	13
9	9	70	11	3

How effective would prophylactic anticonvulsants have to be when given to ICH patients to change your current practice, if they only worked for one of the four outcomes below? To how many ICH patients would you be willing to prescribe prophylactic anticonvulsants if the only benefit was preventing one patient from _____				
2 to 4	5 to 9	10 to 19	20 to 39	40 or more
25	23	22	14	16
16	14	20	19	32
17	7	16	18	42
17	6	10	15	53