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Original Investigation

Antiepileptic Drugs for Patients with Intracerebral Hemorrhage: A Meta-Analysis

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ABSTRACT

AIM: Whether an antiepileptic drug (AED) should be prescribed for intracerebral hemorrhage (ICH) patients is a matter in dispute, and recent studies have come up with different or even opposite views. A meta-analysis on this issue has not been performed. The goal of this meta-analysis was to study antiepileptic drugs' effects on early seizure occurrence and outcome for ICH patients.

MATERIAL and METHODS: We searched the PubMed, Ovid, and Cochrane library until December 2015 to identify relevant articles. A meta-analysis was conducted to evaluate the overall effect with random-effects or fixed-effects models.

RESULTS: Four articles consisting of one randomized controlled trial and three cohort studies met the included criteria. For the occurrence of early seizure, antiepileptic drugs showed the ability to reduce the risk, but reached no statistical significance (OR=0.71; 95% CI, 0.38-1.34; test for overall effect Z=1.06, p=0.29). No association between antiepileptic drug use and poor outcome was found (OR=1.95; 95% CI, 0.56-6.79; test for overall effect Z=1.06, P=0.29), but heterogeneity was present.

CONCLUSION: Summarizing published studies, the AED use did not reduce early seizure occurrence statistically but a population with high-risk factors of early seizure is likely to benefit from AEDs. Besides, AED use was not associated with poor outcome. We suggest AED use for ICH patients with high-risk factors of seizure, but not generally.

KEYWORDS: Intracerebral hemorrhage, Seizure, Antiepileptic drug, Meta-analysis

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH), often along with high mortality and morbidity, is a disaster for the patients. Even surviving through it, patients have to face with various sequelae that seriously affect their life quality. In addition to direct brain damage due to hemorrhage, secondary injuries such as brain edema and post-stroke seizure further deteriorate the patients' condition. Reducing and controlling secondary injures after intracerebral therefore play an important role in patients' recovery.

Referring to the occurrence rate of epilepsy after ICH, data vary widely from 8% to 28% (4,9). The discrepancy between reports may be due to different monitoring methods or omitting non-convulsive epilepsy. Seizures after ICH may predict subsequent epilepsy and poor outcome (10), which lead to a lower threshold for antiepileptic drug use. There is a conditional but not proven practice of applying prophylactic antiepileptic drug (AED) for ICH patients. Meanwhile AEDs may possess neuroprotective effects against hemin toxicity (6), protecting brain cells from deleterious effects after ICH. Exposure to AEDs, however, bring adverse effects such as fever, liver abnormalities, and cognitive dysfunction, depending on the specific medication (12). Even preventing seizures after ICH may not improve outcomes as seizure may not be an independent predicting factor for a better prognosis (3,9).

Whether the prescription of AEDs really improves the prognosis and how to balance the drugs' efficacy and adverse effects to achieve an optimal consequence are still uncertain. We therefore systematically reviewed relevant articles to evaluate the efficacy and safety of prophylactic AEDs in patients in ICH.

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MATERIAL and METHODS

Search Strategy

We searched PubMed, Ovid, and the Cochrane library until December 2015 to identify relevant studies referring to the prophylactic use of AED in ICH patients. Cited references in selected articles were cross-referred in an effort to collect all the published information. We used MeSHs (cerebral hemorrhage, anticonvulsants) combined with free words (brain bleeding, intracranial bleeding, brain hemorrhages, intracranial hemorrhage, hemorrhagic stroke; phenytoin, carbamazepine, valproic acid, phenobarbital) to search in different databases. The detailed search strategy is listed below.

Inclusion Criteria

Two reviewers independently screened the titles and abstracts of all selected material. As for relevant studies, the above two authors read the full articles for including references. Inclusion criteria were:

1) Study investigated patients with primary ICH
2) Intracerebral hemorrhage was diagnosed by a combination of clinical symptoms and imaging results
3) Patients presented with prophylactic or therapeutic AEDs after onset of ICH
4) Patients without AED use in the medical history
5) Compare relevant effect and adverse events between AED and AED-free groups. If more than one study was overlapping or covered the same subjects, only the one with a larger number of patients was included.

In case of disagreements, we referred them to the third author or an independent party.

Outcome Definition

The primary outcome was occurrence of early seizure. Post-stroke seizure occurring within 1 week of ICH onset is defined as early seizure, while epilepsy after 1 week is classified as late seizure (1). Meanwhile early seizure excluded seizures at the onset of ICH. The secondary outcome was the patients' poor prognosis, which was evaluated with different tools and scales in included studies. In this study, to achieve consistent evaluation, we defined poor outcome as follows: modified Rankin scale (mRS)>4, the National Institute of Health Stroke Scale (NIHSS)>14, and need for skilled nursing or death.

Data Extraction

Two authors independently extracted data from each study: first author's name, publication year, specific numbers in the treated or control groups, occurrence of seizures, adverse effects, AED types, patients' outcomes at the endpoint or death.

Statistical Analysis

A pooled odds ratio (OR) and 95% confidence interval (CI) were calculated for dichotomous variables using the Mantel–Haenszel and fixed/random-effects model. Heterogeneity among included studies was measured with Cochrane' Q test and I^2 test, with a threshold of $p<0.10$ indicated heterogeneity. If heterogeneity did not exist ($p>0.10$), a fixed-effects model was applied; otherwise the random-effects model was used. The Z-test was performed for testing overall effect, and $p<0.05$ was considered significant. All the data analysis was performed with "Review Manager 5.3"software.

RESULTS

Search Results

As Figure 1 shows, we identified 978 citations through 3 databases. After excluding 955 articles by screening the abstracts, we evaluated the full text of 23 reports. Eventually we included 4 studies covering 655 patients in data synthesis, consisting of one randomized controlled trial and 3 cohort studies (Table I).

Study Characteristics

There was only one randomized controlled trial (RCT) identified which included 72 patients (4). Considering the number was too small to synthesize data and draw a reasonable conclusion, we included this study in observational studies to evaluate pooled effect.

Though this incorporated method is controversial, several reports have verified its reliability (14,16). Shrier et al. found that the advantages to including both randomized controlled trials and observational studies in meta-analyses outweigh the disadvantages (15). Passero et al. conducted a retrospective cohort study evaluating the occurrence of early seizure in subgroups of ICH location (9). Messe et al. conducted a prospective cohort study, which was the placebo arm of a randomized controlled trial exploring the association between AED use and outcome (7). Reddig et al., as a retrospective cohort study, tried to find out whether ICH patients benefit from AED (11).

Meta-Analysis

Finally four studies with a total of 1285 patients were included in this study. In the pooled analysis, prophylactic AED use seemed to decrease the occurrence of early seizures, but no statistically significant difference was found (OR=0.71; 95% CI, 0.38-1.34; test for overall effect Z=1.06, p=0.29; Figure 2). No substantial heterogeneity existed (I^2=45%).

A poor outcome was not associated with AED use (OR=1.95; 95%CI, 0.56-6.79; test for overall effect Z=1.06, P=0.29; Figure 3). However, an inconsistency existed between studies (I^2=74%), and the random-effects model was applied. Due to too few studies and limited data, we could not conduct meta-regression and subgroup analysis. In the sensitivity analysis, however, each study's influence on the overall meta-analysis result was estimated by repeating the meta-analysis while omitting one study at each turn. Statistically, the same results were obtained, indicating this meta-analysis was stable.

DISCUSSION

Our findings indicated no association between prophylactic

Table I: Characteristics of Included Studies in this Meta-Analysis

Study	Country	Period	AEDs	Follow-up (days)	Mean age (yrs)	Method of detecting seizure
Gilad 2011 (4)	Israel	2003-2008	VPA	365	69.5	Observed and EEG
Messe 2009 (7)	Multicenter	2005	PHT	90	66.1	--
Passero 2002 (9)	Italy	1979-1996	Phenobarbital	30	65.6	Direct observation
Reddig 2011 (11)	USA	2004-2007	LEV, PHT	--	63	Clinical and electrographic

VPA: *Valproic acid,* ***EEG:*** *Electroencephalography,* ***PHT:*** *Phenytoin,* ***LEV:*** *Levetiracetam,* ***USA:*** *United States of America.*

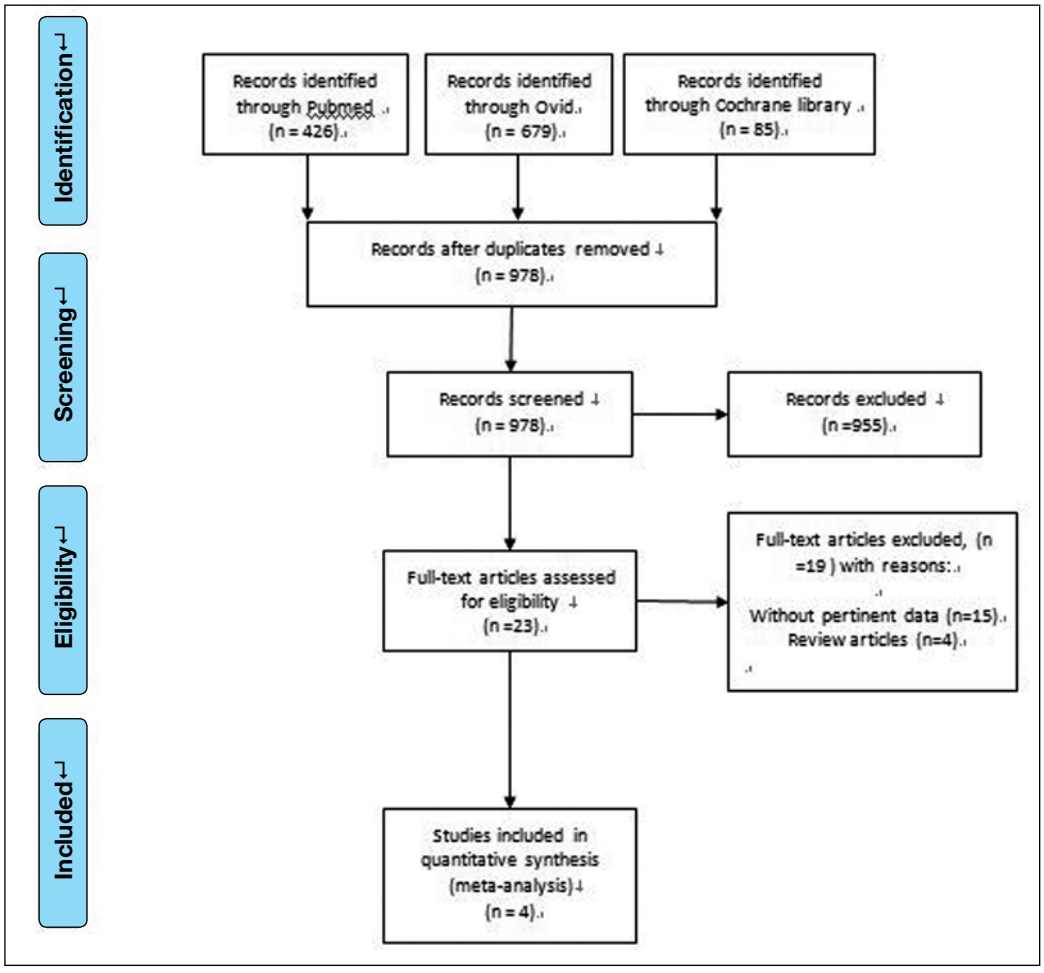

Figure 1: Flow diagram showing selection process of included studies.

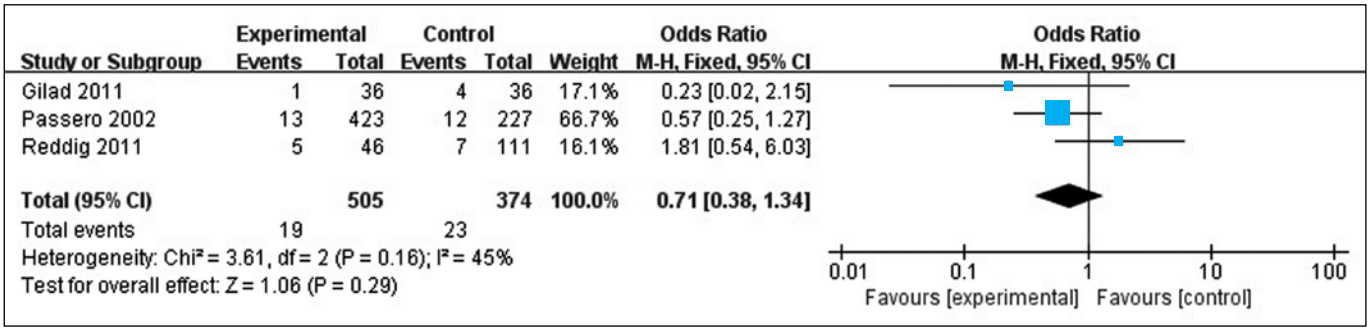

Figure 2: Forest plot depicting pooled odds ratio for early seizure occurrence; p<0.05 is considered statistically significant for Z-test.

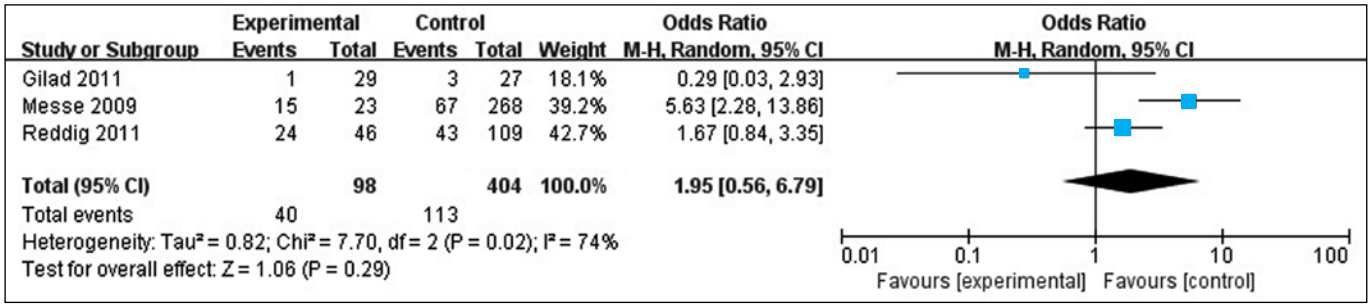

Figure 3: Forest plot depicting pooled odds ratio for poor outcome; p<0.05 is considered statistically significant for Z-test.

AED use and the risk of early seizure, in line with previous studies (8,11).

The mechanism of early seizures is still unclear, and relevant studies mostly focus on cellular biochemical dysfunction and mass effect. Though AED seemed to effectively reduce early seizure occurrence according to clinical experience, we concluded that prophylactic AED use did not reduce this risk. A possible reason is that AED use was not applied randomly, and clinicians were inclined to prescribe AED to patients with high-risk factors of seizure. In observational studies, this confounding factor by indication may lead to bias of early seizure occurrence between control and treatment groups. In a randomized controlled trial (4), a trend toward reduce early seizure incidence was detected compared to the control group, although it did not reach statistical significance. Until now, few RCTs show reduction of early seizure occurrence in patients with prophylactic AED use. The guidelines also do not recommend prophylactic anti-seizure medication for ICH patients (5). Methods of monitoring seizure occurrence were variable, and using continuous EEG is more likely to detect the virtual occurrence rate.

Otherwise, there are some high-risk factors of early seizure, including cortex involvement, lobar ICH, young age and severe stroke. In subgroup or stratified analysis, prescribing AEDs was able to prevent early seizure in ICH patients with high-risk factors (9). Considering that seizures after ICH may lead to secondary bleeding and midline shift (17), preventing seizures is helpful. Therefore, general prescription of AED to ICH patients is irrational, but certain patients with high-risk factors seem to benefit from AEDs.

Our analysis also found that AED use was not associated with a poor outcome. With regard to the relation between AED use and poor outcome, previous studies reported different and even opposite conclusions. Gilad et al.'s mini RCT demonstrated valproic acid treatment improved NIHSS scores in ICH patients, maybe due to valproic acid possessing a neuroprotective effect (4,6). However, several reports indicated AEDs bring about many adverse effects, resulting in poor outcome and even mortality (7,8). Different AEDs and even mixed drug use without dose explanation were presented in included studies, creating an inconsistency in our analysis (I^2=74%, Figure 3), and contributing to application of the fixed-effects model. Sensitivity meta-analysis did not change the result statistically. Except for the included studies, many articles also referred to an association between AED use and poor outcome, but were excluded due to lack of a control group or eligible data. Sheth et al. used the multivariate regression model, proving AEDs could not predict poor outcome (13). A multivariate analysis was also used by Battey et al. (2), arriving at the same result that AEDs were not related with poor outcome. Currently the evidence supporting AEDs' contribution to a poor outcome is not adequate. Combined with our above result, we suggest AED use for ICH patients with high-risk factors of seizure but not generally.

This meta-analysis still had some limitations. First, as an observational studies analysis, unavoidable inherent bias existed. Secondary, unpublished non-English studies were missed, resulting in selection bias. Besides, due to the limited eligible data and information, we could not conduct formal meta-analysis and further subgroup analysis. Many studies have investigated AEDs' predicting effect on the outcome with regression analysis, from which we could not extract specific data (2,8,13). Otherwise, the included studies applied different detection methods and appraisal scales for outcome evaluation, contributing to substantial heterogeneity. Most importantly, there is no high quality RCT or big sample number cohort study for analysis. Despite the above shortages, the strength of this meta-analysis outweighed its limitations. There are very few meta-analyses assessing AEDs' effect on ICH patients. Our analysis synthesized existing data to draw valuable conclusions, in an attempt to solve controversial issues and urge further RCTs. Though substantial heterogeneity existed, sensitivity analysis did not change the result statistically, indicating reliability of the result.

CONCLUSION

AED use is not associated with reduced early seizure occurrence rate and poor outcome, though a population with high-risk factors of early seizure will likely benefit from AEDs. Prescribing AEDs for certain high-risk patients is reasonable and clinically feasible.

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