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Impact of antiepileptic drugs for seizure prophylaxis on short and long-term functional outcomes in patients with acute intracerebral hemorrhage: A meta-analysis and systematic review☆

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ABSTRACT

Purpose: The purpose of this analysis is to assess the effect of antiepileptics (AEDs) on seizure prevention and short and long term functional outcomes in patients with acute intracerebral hemorrhage.

Method: The meta-analysis was conducted using the PRISMA guidelines. A literature search was performed of the PubMed, the Cochrane Library, and EMBASE databases. Search terms included "Anticonvulsants", "Intracerebral Hemorrhage", and related subject headings. Articles were screened and included if they were full-text and in English. Articles that did not perform multivariate regression were not included. Overall effect size was evaluated with forest plots and publication bias was assessed with the Begg's and Egger's tests.

Results: A total of 3912 articles were identified during the initial review. After screening, 54 articles remained for full review and 6 articles were included in the final analysis. No significant association between the use of AEDs after ICH and functional outcome (OR 1.53 [95%CI: 0.81–2.88] P = 0.18, I^2 = 81.7%). Only one study evaluated the effect AEDs had in preventing post-ICH seizures.

Conclusions: The use of prophylactic AEDs was not associated with improved short and long outcomes after acute ICH. This analysis supports the 2015 AHA/ASA recommendation against prophylactic AEDs (class III; level of evidence b).

1. Introduction

Intracranial hemorrhage (ICH) is one of the most devastating forms of stroke with a reported mortality rate of up to 50% in the literature. [1] One complication is the development of seizures that occurs in 2%–40% of patients post-ICH. The significant variation in incidence is related to the type and duration of monitoring, length of follow-up, and patient characteristics including hemorrhage volume, hemorrhage location, and cortical involvement [2–12].

Prophylaxis against seizures in patients with acute ICH remains controversial. It is unclear if the possible acute and long-term benefits of seizure prevention with antiepileptic drugs (AEDs) outweigh the risk of potential adverse drug effects. [13] To date, evaluation of the efficacy and safety of prophylactic AED use in patients with ICH has been mostly limited observational studies. In light of such modest clinical evidence and yet concern for the detrimental effects of seizures in this population, seizure prophylaxis with AEDs is commonly practiced. [14–16] This treatment algorithm remains popular despite the most recent ICH guidelines from the AHA/ASA (based on their experts' assessment of this limited data set) recommending that "prophylactic anticonvulsant medication should not be used" [17]. Thus, considerable controversy exists, and without a large, randomized, placebo-controlled trial, a comprehensive evaluation of current literature is warranted. We therefore conducted a meta-analysis to assess whether the use of AEDs is associated with improved functional outcomes in patients with ICH, or conversely if they confer significant risk and to evaluate their impact

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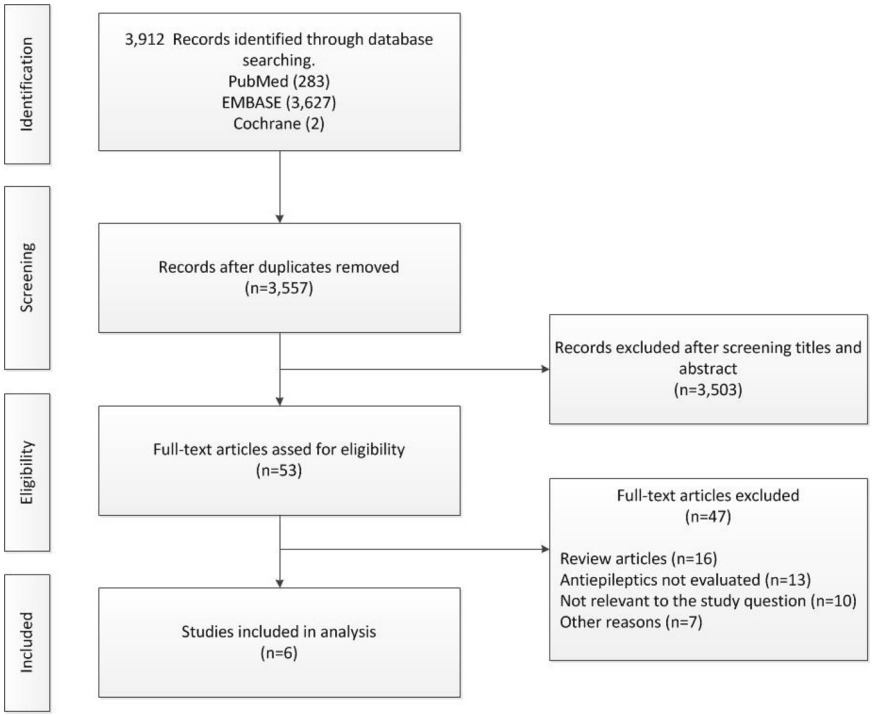

Fig. 1. Flow of Articles Reviewed.

on seizure prevention.

2. Methodology

This systematic review and meta-analysis was reported according to the recommendations of the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) assessment [18].

2.1. Search strategy

We performed a search of MEDLINE (January 1990 to December 2017), EMBASE (January 1990 to December 2017), and the Cochrane Library (January 1990 to December 2017) to identify literature that evaluated AEDs for seizure prophylaxis in patients with intracerebral hemorrhage. PubMed, EMBASE, and the Cochrane library were searched using MeSH terms, explored EMTREE headings, and keywords respectively. Search terms and Boolean operators included the combination of "anticonvulsants" or "antiepileptics" with "brain hemorrhage" or "intracerebral hemorrhage". A detailed search strategy is described in Supporting File 1. The results were cross-referenced to identify any additional literature.

2.2. Study selection

Two researchers conducted the database searches independently, as well as screened and evaluated the article titles and abstracts. A third researcher (L.R.L.) was employed in the case of disagreements. Articles were excluded during the screening process if they were not relevant to the use of AEDs in intracerebral hemorrhage or evaluated seizure prophylaxis in other clinical conditions such as subarachnoid hemorrhage. Duplicate records, case-reports, reviews, and non-English articles were also excluded.

Observational or randomized studies were included in the meta-analysis if they compared the use of AEDs for seizure prophylaxis to no pharmacologic prophylaxis in acute ICH. Observational studies that did not perform multivariate analysis were excluded. Seizure prevention and long-term outcomes, as defined by a modified Rankin Score (mRS) at 3 months or greater were evaluated. Data extracted from the articles included year of publication, type of study, sample size, definition of outcomes, effect size of the association between AED use and outcomes, and confounding factors included in the multivariate analysis.

2.3. Quality assessment

The quality of the randomized trials included in this meta-analysis was assessed by the Cochrane review criteria, and for nonrandomized studies, the Modified 11-item Methodological Index for Nonrandomized Studies tool (Supporting File 2), was used. [19] For randomized trials, the score was calculated for each randomized trial based on seven items (random sequence generation, allocation concealment, blinding of personnel who administered AEDs, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias). Each item was scored between 2 and 0 (being 2 "positive", 1 "unclear", 0 "negative"). For nonrandomized trials, 11 items were scored: 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 22 using this modified tool for quality assessment. Studies with a score with 18 or higher were considered to be of high methodological quality, while studies between 10 and 17 were considered moderate. Studies with a score less than 10 were not included.

2.4. Statistical analysis

We constructed forest plots to illustrate the estimations and overall effect sizes. Heterogeneity was assessed by (I [2]) with the correspondent chi-squared test (I [2] < 50% and I^2 > 50% were considered insignificant and significant heterogeneity, respectively). Publication bias was calculated using Stata version 13.0 (Stata, College Station, TX) with the Begg's and Egger's test. [16] Funnel plots were constructed to represent any tendency for publishing in favor to the positive effect. Significant publication bias was considered when there was asymmetry in the funnel plot (meaning that smaller studies tend to show larger risk ratios [RR]) and a statistically significant bias coefficient according to the Egger's test [16]. P values < 0.05 were considered as statistically

Table 1
Description of studies included in this meta-analysis for poor functional outcomes.

Study	Year	Type of study	Population	Comparison	AED prophylactic drug	Outcome	Multivariate model	Effect size (95%CI)
Battey et al. [20]	2012	Prospective cohort	ICH (1182)	AED use (46%) vs. no use	Phenytoin (68%) Levetiracetam (30%) Valproic acid (1%) Carbamazepine (1%)	90-day post-ICH mortality Poor outcome at 3 months (mRS ≥ 4)	Age, sex, length of hospital stay, baseline ICH volume, hypercholesterolemia, hypertension, atrial fibrillation, previous hemorrhage, intraventricular hemorrhage (IVH), warfarin use	OR = 0.62, (0.42–0.90) OR = 0.69, (0.50–0.94)
Gilad et al. [21]	2016	Randomized controlled trial	ICH (72)	AED use (50%) vs. no use	Valproic acid (100%)	Poor outcome at one year (NIHSS ≥ 15)	Age, GCS, IVH, ICH score, seizure, AED use	OR = 1.33, (0.78-2.26) P = 0.29
Messe et al. [22]	2009	Multicenter randomized trial	ICH (295)	AED use (8%) vs. no use	Phenytoin (78%) Valproate (17%) Lamotrigine (4%)	Poor outcome at 3 months (mRS ≥ 5)	Age, hematoma volume, IVH, GCS, prior warfarin use, AED use	OR = 6.83 (2.20-21.23)
Naidech et al. [9]	2009	Prospective cohort	ICH (98)	AED use (42%) vs. no use	Levetiracetam (30%) Phenytoin (55%) Phenytoin + levetiracetam (6%) Others: gabapentin, oxcarbazepine, topiramate	Poor outcome at 3 months (mRS ≥ 4)	Admission NIHSS, age	OR = 9.8 (1.4-68.6)
Sheth et al. [23]	2015	Retrospective cohort	ICH (744)	AED use (39%) vs. no use	Levetiracetam (85%) Phenytoin (11%) Phenytoin + levetiracetam (4%)	Poor outcome at 3 months (mRS ≥ 4)	Ethnicity, gender, age, ICH volume, IVH, admission GCS.	OR = 1.11 (0.74 – 1.65)
Zandieh et al. [14]	2016	Retrospective cohort	ICH (802)	AED use (10%) vs. no use	Phenytoin (58%) Valproate (17%) Levetiracetam (4%) Carbamazepine (7%) Multiple AEDs (11%)	Poor outcome at 3 months (mRS ≥ 3)	Age, GCS, ICH volume, IVH, ICH score, seizure, AED	OR 1.66 [1.04-2.66] for any AED. OR 1.97 [1.06-3.67] Phenytoin prophylaxis

Abbreviations: AED anti-epileptics; GCS Glasgow Coma Score; ICH intracerebral hemorrhage, mRS modified Rankin scale; NIHSS National Institutes of Health Stroke Scale; OR odds ratio.

significant in all statistical analyses. The meta-analysis was performed using Stata 13.0 (Stata, College Station, TX) with random-effect model (DerSimonian & Laird method). [17]

3. Results

3.1. Literature search results

A total of 3912 articles were identified using our search strategies. The initial screening process identified 54 articles for review. Of these, 6 studies met inclusion criteria for analysis. Fig. 1 shows the diagram of the article selection.

3.2. Study characteristics

In total 6 studies were included in this meta-analysis (two retrospective cohort studies, two prospective cohort studies, and two randomized controlled trials). The studies comprised a total of 3193 patients. Table 1 summarizes the characteristics of the studies included in the analysis. The results of the methodological quality assessment are shown in Supporting File 3. The quality assessment criteria ranged from 13 to 18 points for evidence synthesis.

3.2.1. Association of the use of AEDs on long term outcomes after ICH

We found no evidence of significant association between the use of AEDs after ICH and functional short and long-term (≥3 months to one year) outcome, defined by modified Rankin scale (mRS) of greater than or equal to 3 or the National Institute of Health Stroke score (NIHSS) of 15 or greater (OR 1.53 [95%CI: 0.81–2.88] P = 0.18, I [2] = 81.7%). In the 5 studies in which the follow-up period was 3 months there was no statistically significant association between using AEDs in ICH and functional outcome (OR 1.70 [95% CI: 0.88–3.28], P = 0.11, I [2] = 84.7%). This was also demonstrated in the analysis by Gilad et al which followed subjects out to 1 year (OR 0.31 [95% CI: 0.03–3.17], P = 0.32) [21]. Fig. 2] shows the forest plot of the main analysis. Sensitivity analysis demonstrated that our results do not vary significantly after excluding each study and therefore it do not depend on individual studies.

3.2.2. Association of the use of AEDs and seizure prevention after ICH

We found only one study that investigated the association between the use of AEDs and seizure prevention using a multivariate analysis (Table 2). In this prospective study of 761 patients, lobar location of the ICH was the only independent risk factor for development of clinical seizures during the first 30 days after ICH, aOR 2.8 (1.63–4.82). [10] Prophylactic phenobarbital decreased the risk of clinical seizures in the first 30 days after ICH, aOR 0.58 (0.39 – 0.87). However, this finding must be interpreted with caution as it was a non-randomized, observational study.

3.2.3. Publication Bias and heterogeneity

There was no evidence of publication bias in the analysis (Egger's bias = 2.23, P = 0.23). Funnel plots are shown in Figs. 3 and 4.

3.3. Discussion

This meta-analysis evaluated 6 studies that assessed the use of seizure prophylaxis in patients with spontaneous ICH. Our results suggest that the use of prophylactic AED is not associated with improved short and long-term functional outcomes. The only study investigating the effect of AED on seizures post-ICH identified a benefit of AEDs on seizure prevention in the first 30 days after ICH, however this was a non-randomized, observational study and therefore confounding bias may be present.

Our results confirmed a prior meta-analysis results that found no benefit of AED use in ICH. [29] However, our analysis evaluated a greater number of studies (6 vs 4) and included significantly more patients (3193 vs 1285). In the prior meta-analysis the authors extracted data using univariable analysis without adjusting for potential confounding variables, while we extracted data only from studies with a multivariate analysis. The use of adjusted datasets is one of the strengths of this meta-analysis because it increases the validity and consistency of our results. In addition, there was no evidence of publication bias according to Egger's and Begg's tests.

The reported rate of seizures in patients with ICH varies greatly and can occur in up to 40% of patients; seizures may be associated with lobar and cortical lesions. [2,30–32] The impact of seizures on clinical outcomes is not well elucidated but varies due to significant heterogeneity within the patient populations. [32–34] Given the unclear risk of seizures after ICH and presumed deleterious effects of seizure on outcomes in critically ill patients, the use of AEDs for seizure prophylaxis is likely extrapolated from data in traumatic brain injury, aneurysmal subarachnoid hemorrhage, craniotomies, and intracerebral tumors. [35,36] We identified only one study that evaluated the effect of AEDs and the risk of seizures, phenobarbital was shown to reduce the risk of clinical seizures (OR: 0.58 [95% CI: 0.39 – 0.87]) [10]. The study, however, did not find the occurrence of early seizures to be associated with worse outcomes, or late-onset seizures.

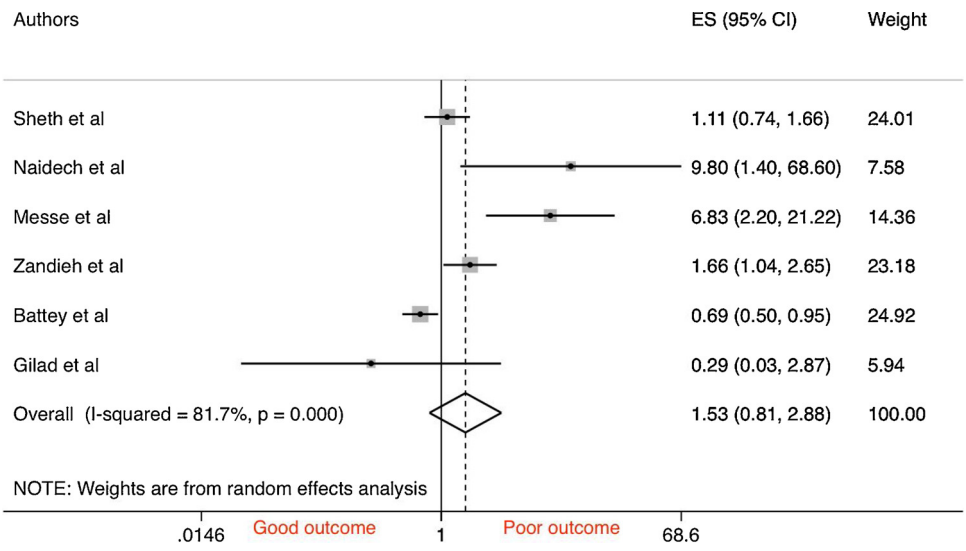

Fig. 2. Forest plot for effect size evaluating the use of antiepileptic drugs with outcome defined as modified Rankin scale at 3 months or more.

Table 2
Description of other studies that investigated the association between the use of antiepileptic drugs (AED) and other outcomes (i.e. seizures), not included in the meta-analysis due to lack of multivariate models and the small number of studies.

Study	Year	Type of study	Population	Comparison	AED prophylactic drug	Outcome	Multivariate model	Effect size (95%CI)
Biffi et al. [[24]]	2016	Prospective cohort	ICH (872)	No comparison			No multivariate model	
Hashim et al. [25] (poster)	2012	Retrospective cohort	ICH, aSAH	Phenytoin vs. levetiracetam	Phenytoin, Levetiracetam	Poor outcome at 3 months	No multivariate model	
Passero et al. [10]	2002	Prospective cohort	ICH (761)	AED use vs. no use	Phenobarbital	Seizures within 30 days of ICH	Age, midline shift, larger hematoma, location	OR = 0.58, (0.39-0.87)
Rapaport et al. [26] (abstract)		Retrospective cohort	ICH (174)	AED use vs. no use	Not specified	ICH-related seizures	No multivariate model	
Reddig et al [13]	2011	Retrospective cohort	ICH (157)	AED use vs. no use	Phenytoin, Levetiracetam	ICH-related seizures	No multivariate model	
Srinivasan et al. [15]	2013	Retrospective cohort	ICH (138)	AED use vs. no use	Not specified	ICH-related seizures	No multivariate model	
Taylor et al. [27]	2010	Retrospective cohort	ICH (269)	Phenytoin vs. levetiracetam	Phenytoin, Levetiracetam	Cognitive function	No multivariate model	
Claessens et al [28]	2017	Retrospective cohort	ICH (783)	AED use vs. no use	Not described	Mortality	Cox Regression	

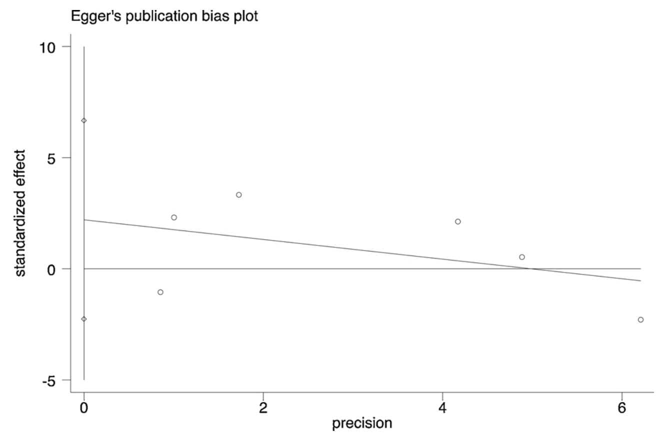

Fig. 3. Egger's funnel plot of the included studies that assess the effect of antiepileptic use on poor outcome in patients with intracerebral hemorrhage.

Only a few small trials have evaluated the impact of AEDs on functional outcomes in ICH. Two studies published in 2009 found a significant association between AED initiation and poor outcomes defined as an mRS of 5–6 (OR: 9.8 [95% CI: 1.4–68.6]) and 4–6, respectively (OR: 6.8 [2.2–21.2]). [9,22] Several subsequent studies, however, have not confirmed this association [20,21,23]. Our results suggest that AED use is not associated with improved outcomes (Fig. 2). There are several considerations when interpreting these data. All studies but one were observational in design, and the lack of randomization leads to an inherent bias. The studies used older AED with more side effects and drug interactions than the ones currently available on the market. Other important outcomes have not been investigated like risk for epilepsy, hospital stay, cognitive and psychiatric outcomes. Lastly, providers may have selectively used prophylaxis in patients that were at a higher risk. For example, the rate of lobar hemorrhages, a significant risk factor for seizures, was frequently higher in the AED-treated groups. [9,20,22,23]

In addition to diverse patient characteristics, variability of AED selection and use may have contributed to the differences observed within the studies (Table 1). The use of AEDs ranged between 8 and 46% between the observational studies and most frequently consisted of phenytoin, levetiracetam, and valproate. Choice of AED may have a particular large impact on benefit and risk. Four studies reported phenytoin as the predominant AED used, of which three demonstrated poor outcomes. [9,14,20,22] Sub-analyses in two of those studies, found phenytoin was associated with worse and no effect on outcomes (OR: 9.8 [95% CI: 1.4–68.6]; OR: 0.63 [95% CI: 0.31–1.29]). In the same studies, levetiracetam was neutral when adjusted for patients who survived more than 5 days. These data suggest that phenytoin may have a detrimental effect on functional outcomes, consistent with data from prior studies on aneurysmal subarachnoid hemorrhage [37]. Our results neither demonstrate a risk nor benefit of AED prophylaxis in ICH. This analysis supports the 2015 AHA/ASA recommendation against prophylactic AEDs (class III; level of evidence b) [38].

Despite the paucity of data, the use of prophylactic AEDs in ICH has increased in recent years and may be practice in as many as 40% of patients. [23,39] A multi-center, observational study found the rate of prophylactic AED in ICH doubled from 2007 to 2012.39] This increased use of seizure prophylaxis has been associated with a preferential use of levetiracetam and a stark reduction in phenytoin [23,39]. Experts have postulated that the improved adverse event and drug interaction profile have led to the increase in levetiracetam use [40]. While levetiracetam has not been shown to have any clinical relevant drug interactions in neurocritical care patients, it should not be considered a benign drug [41]. Patients are at increased risk of agitation, psychosis, and somnolence [42]. This uncertainty calls for a large, multicenter, randomized controlled trial evaluating the use of AED for seizure prophylaxis,

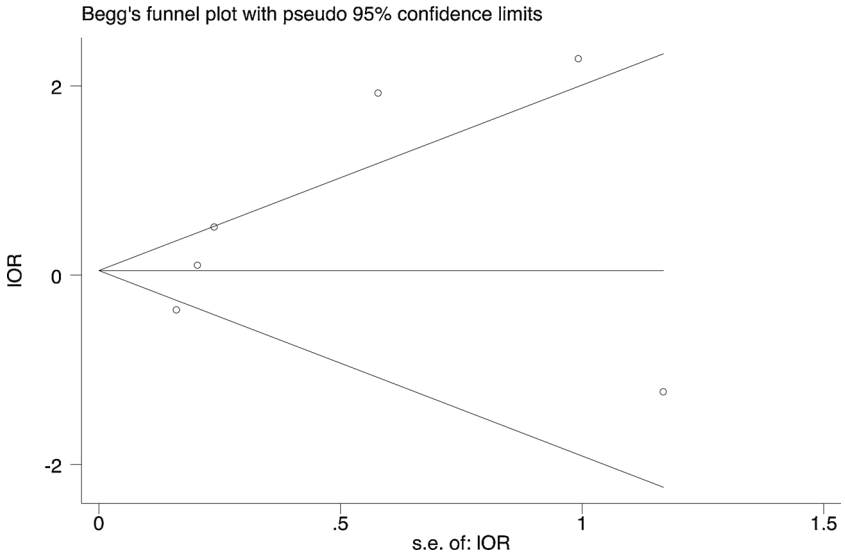

Fig. 4. Begg's funnel plot of the included studies that assess the effect of antiepileptic use on poor outcome in patients with intracerebral hemorrhage.

and of the long- term functional and cognitive outcomes after ICH.

3.4. Limitations

Our analysis has several limitations. First, the majority of the published data included in this meta-analysis was from retrospective observational studies introducing an inherent risk of bias. Our analysis of publication bias analysis is inconclusive because of the limited data points. We limited our results to full-text articles written in English; several studies were only available as abstracts. Abstracts were excluded because multivariate data could not be extracted. Another limitation of our results was the significant heterogeneity, which may be due to differences between patients, study design, factors controlled for, and choice of AED therapy. Finally, the effect of different AEDs or targeted interventions in high risk patients remains unknown. Analysis of patient level data would have provided a more robust evaluation.

4. Conclusion

This meta-analysis indicates that AED use in ICH is not associated with improved functional short and long outcomes. This analysis supports the 2015 AHA/ASA recommendation against prophylactic AEDs. The advantage of one AED over another, or their use in high-risk patients (e.g. with lobar hemorrhage) remains unknown. However, any benefit of AED prophylaxis on long-term outcomes would be marginal as the effect of seizures on outcomes remains small. A large prospective randomized-controlled trial is needed to better demonstrate the effects of newer generation AEDs in patients with ICH on cognitive, psychiatric and functional outcomes.

Author contributions

Brian Spoelhof, PharmD: Design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content

Julian Sanchez-Bautista, MD: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content

Andres Zorrilla-Vaca, BSc: analysis or interpretation of the data

Peter W. Kaplan, MBBS, FRCP: drafting or revising the manuscript for intellectual content

Salia Farrokh, PharmD: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content

Marek Mirski, MD, PhD: drafting or revising the manuscript for intellectual content

Brin Freund, MD: drafting or revising the manuscript for intellectual content

Lucia Rivera-Lara, MD, MPH: Design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content

Author disclosures

Dr. Spoelhof has nothing to disclose.
Dr. Sanchez-Bautista has nothing to disclose.
Mr. Zorrilla-Vaca has nothing to disclose.
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Dr. Farrokh has nothing to disclose.
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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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