Systematic Review and Meta-Analysis

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Efficacy of levetiracetam compared with phenytoin in prevention of seizures in brain injured patients

A meta-analysis

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Abstract

Background: Early and/or late onset in patients with brain injury (BI) is associated with a poorer prognosis, and phenytoin (PHT) is standard of care to prevent seizures. Levetiracetam (LEV), an alternative antiepileptic drug, is associated with less cognitive disruption. The purpose of this study was to evaluate the safety and efficacy of LEV in the prevention of brain traumatic seizures with the standard drug PHT.

Methods: Search the publications on comparison the safety and efficacy of LEV against the standard agent PHT in prevention of traumatic seizures in BI to January 2018. After rigorous reviewing on quality, the data were extracted from eligible trials. All trials analyzed the summary hazard ratios of the endpoints of interest.

Results: LEV was found not more effective than PHT in terms of overall seizure (odds ratio [OR] = 0.73; 95% confidence interval [CI] = 0.51–1.05; $P = .09$), and late seizure (OR = 0.64; 95% CI = 0.34–1.19; $P = .16$) occurrence. However, there is significant difference in terms of early seizure (OR = 0.63; 95% CI = 0.40–0.99; $P = .04$). Moreover, there were no significant differences in terms of mortality (OR = 0.67; 95% CI = 0.43–1.05; $P = .08$), or side effects (OR = 1.31; 95% CI = 0.80–2.15; $P = .29$) between groups.

Conclusion: The meta-analysis showed that LEV prevention of seizures was associated with early seizure rates that were lower than the PHT-prolonged course of treatment. There is no statistically significant difference in the efficacy and safety profile of PHT and LEV in cases of traumatic BI.

Abbreviations: BI = brain injury, LEV = levetiracetam, PHT = phenytoin.

Keywords: brain injury, levetiracetam, meta-analysis, phenytoin, seizure

1. Introduction

The mechanical forces in head injured patient affect the functional outcome neuronal and vascular tissue at the time of impact. A series of pathologic events may have adverse effects on the patient's neurologic state of brain damage and worsen their clinical outcomes.[1] Seizures are common in patients with head injuries and are often associated with adverse outcomes.[2,3] The control of posttraumatic seizure is mandatory because these acute insults may increase in secondary injuries to the already damaged brain,[4] which alter intracranial pressure, rebleeding, and oxygen delivery to cerebral tissue.[5,6]

To reduce the risk of the seizure, the use of prophylactic antiepileptic drugs (AEDs) are routinely used in this setting.[7] Traditionally, phenytoin (PHT) has been found as a sodium channel blocker since 1938 and accepted as the most commonly used drug to prevent seizures in terms of its effectiveness.[8] However, it has many side effects (SEs), including cardiac events that may cause serious complications.[9,10] Therefore, the new AED is increasing be studied to find the better AED as a perioperative prophylactic drug.[11]

Levetiracetam (LEV) is a novel AED with different pharmacologic characteristics from PHT.[1] PHT has no liver metabolism and has no known effect on the kinetics of other drugs.[12,13] The use of LEV has recently become popularized because there is no need to monitor serum levels and better tolerability compared with PHT. Additionally, previous studies have reported that LEV has been associated with considerable neuroprotective properties in both epileptic and nonepileptic disorders.[14–16] This has made LEV a popular alternative to PHT in the treatment of epilepsy patients.

Although the prevention of seizures and relapses in patients with brain injury (BI) may improve their prognosis, studies comparing LEV and PHT have produced conflicting results.[16,17] With regard to the indications for antiepileptic prevention, significant differences in the manner and duration are still

Editor: Bernhard Schaller.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2018) 97:48(e13247)

Received: 23 July 2018 / Accepted: 19 October 2018

http://dx.doi.org/10.1097/MD.0000000000013247

noticed. The purpose of our study was to evaluate the efficacy and safety of PHT and LEV in preventing early and/or late seizures in patients with BI.

2. Methods

2.1. Search strategy

Two independent investigators searched electronic databases: Pubmed, Embase, and Cochrane library up to January 2018. The following search items were used: "Levetiracetam," "Phenytoin," "Seizure," AND "Brain injury." And relevant Medical Subject Heading (MeSH) terms were utilized. References cited in the publications were hand-searched to identify additional relevant publications. Ethics approval was waived because this is a meta-analysis on published data with no human participants or animals.

2.2. Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: articles that enrolled patients with BI; the

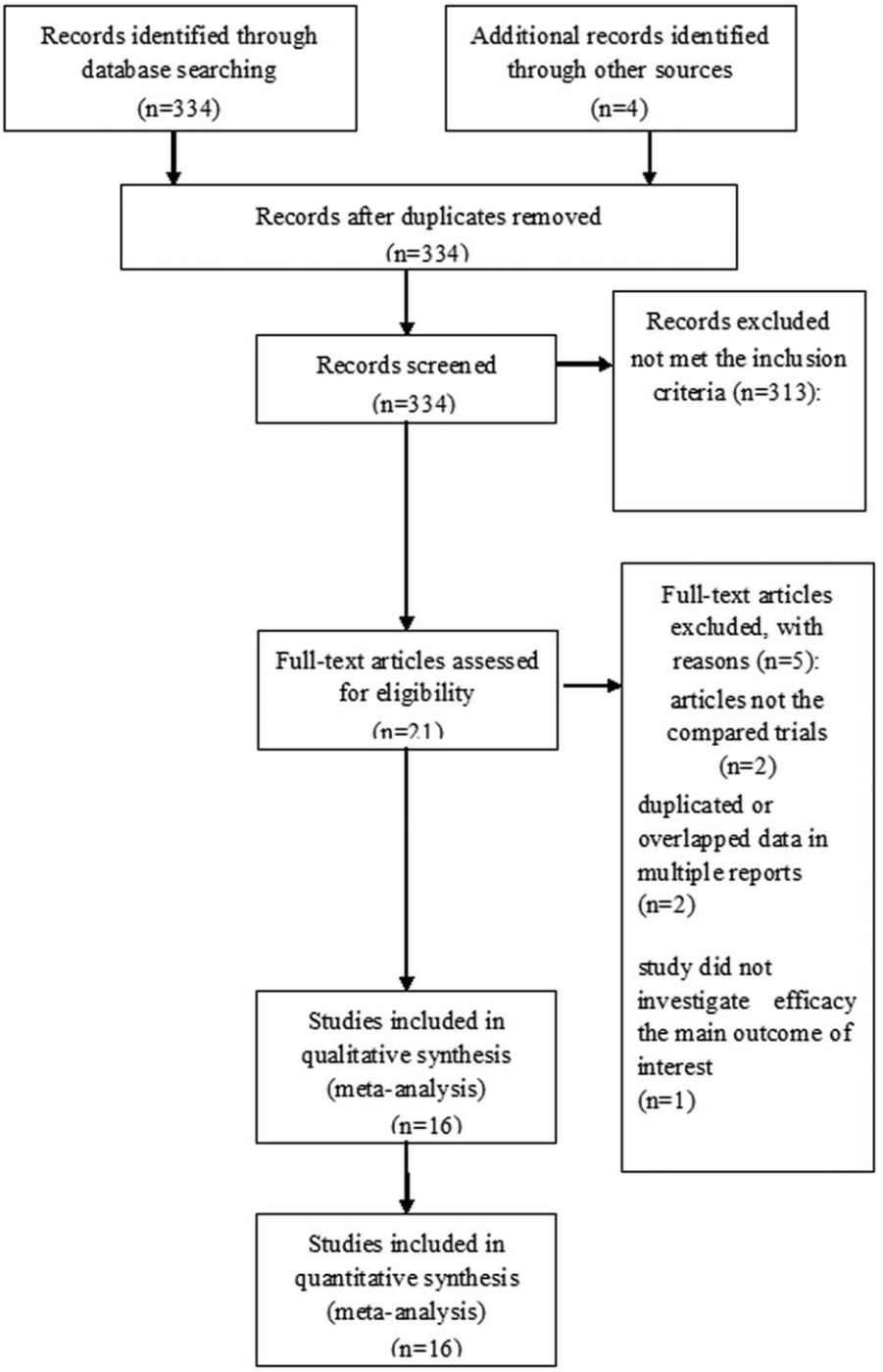

Figure 1. PRISMA flow chart of selection process to identify studies eligible for pooling.

Table 1

Illustration of the main features of the eligible studies in more detail.

Author, y	Study type	Patients, n		Patient population
		LEV	PHT	
Jones, 2008	Non-RCT	32	41	Traumatic brain injury
Milligan, 2008	Non-RCT	105	210	postcraniotomy
Lim, 2009	RCT	15	8	Glioma/postcraniotomy
Szaflarski, 2010	RCT	34	18	Traumatic brain injury/subarachnoid Hemorrhage
Taylor, 2010	Non-RCT	60	25	intracranial hemorrhage
Murphy-Human, 2011	Non-RCT	145	297	Subarachnoid hemorrhage
Inaba, 2013	RCT	406	407	Traumatic brain injury
Kruer, 2013	Non-RCT	20	89	Traumatic brain injury
Caballero, 2013	Non-RCT	18	72	Traumatic brain injury
Fuller, 2013	RCT	36	38	Postcraniotomy
Gabriel, 2014	Non-RCT	5	14	Traumatic brain injury
Radic, 2014	Non-RCT	164	123	intracranial hemorrhage
Iuchi, 2015	Non-RCT	52	58	Brain tumor/postcraniotomy
Shahbaz, 2016	Non-RCT	77	77	traumatic brain injury
Bansal, 2014	Non-RCT	48	35	Traumatic brain injury/intracranial hemorrhage
Kern, 2012	Non-RCT	81	154	Postcraniotomy

LEV = levetiracetam, PHT = phenytoin, RCT = randomized clinical trial.

studies are designed as comparing LEV to PHT for seizure prophylaxis; studies providing data of on clinical interested results, and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were provided; and all publications are limited to using English. If we found duplicated or overlapped data in multiple reports, we just include the one with most complete and latest data.

2.3. Quality assessment

Two investigators independently assessed the quality of the search. We use the Newcastle-Ottawa Quality Assessment Scale recommended by the "Cochrane Intervention Manual Systematic Review."

2.4. Data extraction

Two researchers independently extracted the following information from each study. Disagreements have been resolved through consensus. From each eligible study, the following information was collected: author's name; year of publication; type of study; baseline characteristics of the patient; number of patients; and outcome data for each group of interest.

2.5. Statistical analysis

Odds ratios (ORs) and their 95% CIs combined to assess the safety and efficacy of PHT and LEV in preventing seizures, including seizure rate, mortality, and incidence of serious adverse events. The endpoints of interest in the pooled analysis were ORs and 95% CIs. The endpoints were considered to be a weighted average of the estimated individual HRs for each of the included studies, using the reciprocal method of variance.

Sensitivity analyses were also performed to examine the effect on overall outcomes, depending on the heterogeneity among the included studies. Heterogeneity was investigated by use of the I^2 statistic.[18] I^2 value >50% suggested high degree of heterogeneity, and <50% were considered to have low heterogeneity.[19] The fixed effect model was used only when the heterogeneity in the study was low. At the same time, the remaining pooled HRs

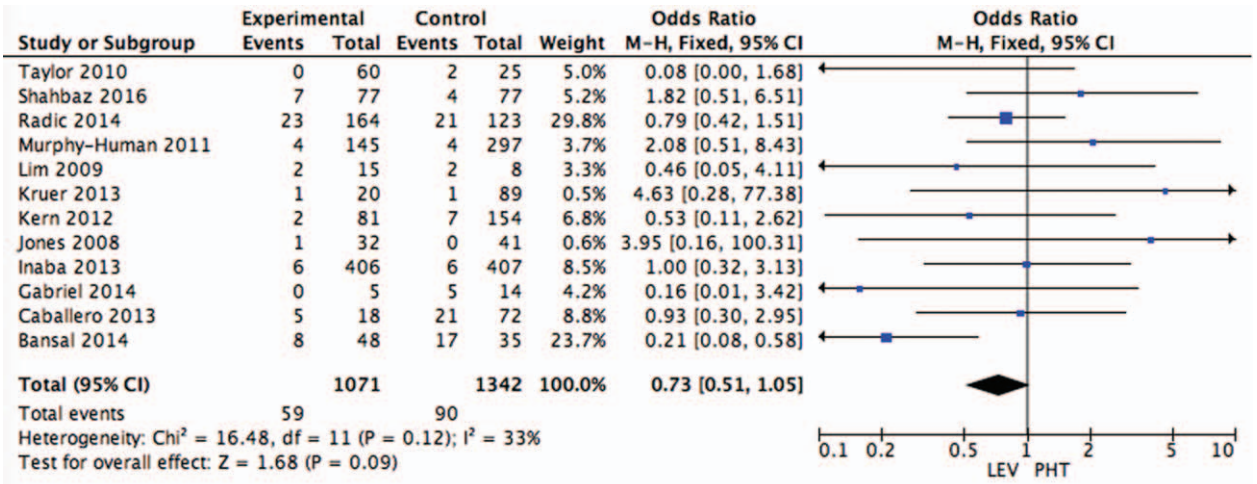

Figure 2. Pooled analysis of incidence of overall seizures between levetiracetam (LEV) therapy and phenytoin (PHT) therapy.

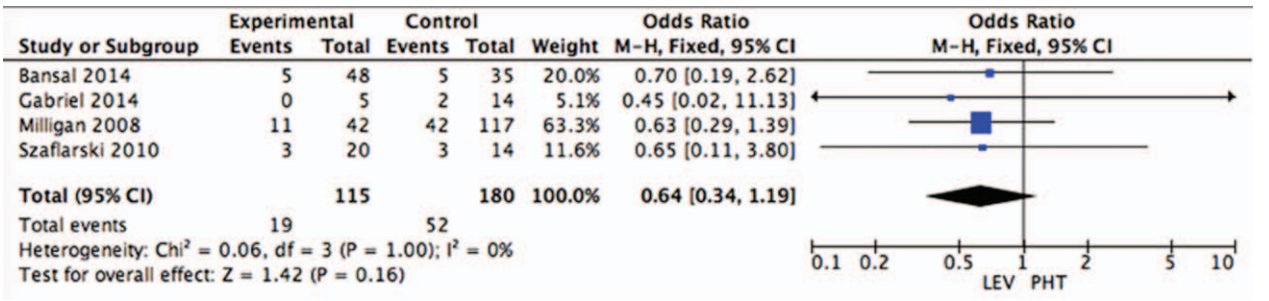

Figure 3. Pooled analysis of incidence of late seizures between levetiracetam (LEV) therapy and phenytoin (PHT) therapy.

were calculated using a random effects model. *P*-values <.05 were considered statistically significant. Statistical analysis was performed using Review Manager Version 5.3 software (Revman; The Cochrane Collaboration, Oxford, UK). Our meta-analysis results are displayed in forest plots.

3. Results

3.1. Overview of literature search and study characteristics

A total of 334 studies were retrieved initially for evaluation. Based on the criteria described in the methods, 21 publications were evaluated in more detail, but 5 did not meet the inclusion criteria. Therefore, a final total of 16 studies with included.[1,16,17,20–30] The search process is described in Figure 1.

All included studies in this study were considered to be of moderate quality at least. Table 1 describes the primary characteristics of the eligible studies in more detail.

3.2. Clinical and methodologic heterogeneity

3.2.1. Pooled analysis of incidence of seizures between LEV therapy and PHT therapy. For the incidence of seizures, no significant differences compared LEV therapy and PHT therapy were observed in terms of overall seizure (OR = 0.73; 95% CI = 0.51–1.05; *P* = .09) (Fig. 2), and late seizure (OR = 0.64; 95% CI = 0.34–1.19; *P* = .16) occurrence (Fig. 3). However, there is significant difference of early seizure (OR = 0.63; 95% CI = 0.40–0.99; *P* = .04) (Fig. 4).

3.2.2. Pooled analysis of mortality between LEV therapy and PHT therapy. A fixed-effects model was used to pool the mortality data, since the heterogeneity across the 4 studies was not significant.[16,24,25,28] The pooled data showed that LEV therapy did not reduce mortality rate (OR = 1.31, 95% CI = 0.80–2.15, *P* = .29) than PHT therapy (Fig. 5).

3.2.3. Pooled analysis of SEs between LEV therapy and PHT therapy. The pooling SEs data[24–26,30] did not achieve advantage in the LEV therapy (OR = 0.67, 95% CI = 0.43–1.05, *P* = .08). In other words, LEV therapy compared to PHT therapy did not reduce the rate of SEs (Fig. 6).

4. Discussion

Seizures encountered in BI patients are commonly because of high intracranial pressure or because of any irritating supratentorial lesion which may be associated with increased mortality and worse clinical outcome.[31–33] The occurrence of posthemorrhagic seizure increase the secondary injuries, which is associated with longer intensive care unit stay, increase the cost of treatment, complications in treatment of intracranial hemorrhage, hypoxia, increased edema, and midline shift.[34]

To the best of our knowledge, the high incidence of seizures after acute BI has led to the development of posttraumatic epilepsy. The secondary damage from epilepsy have promoted the use of prophylactic AEDs in this situation.[7] Despite the important to prevent the seizures, the role of AEDs still remains controversial.

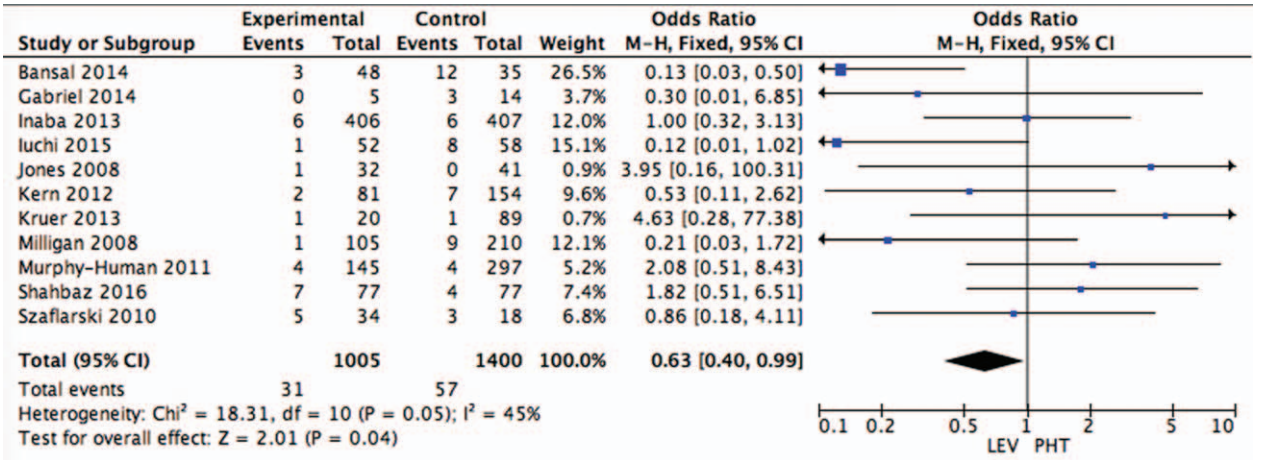

Figure 4. Pooled analysis of incidence of early seizures between levetiracetam (LEV) therapy and phenytoin (PHT) therapy.

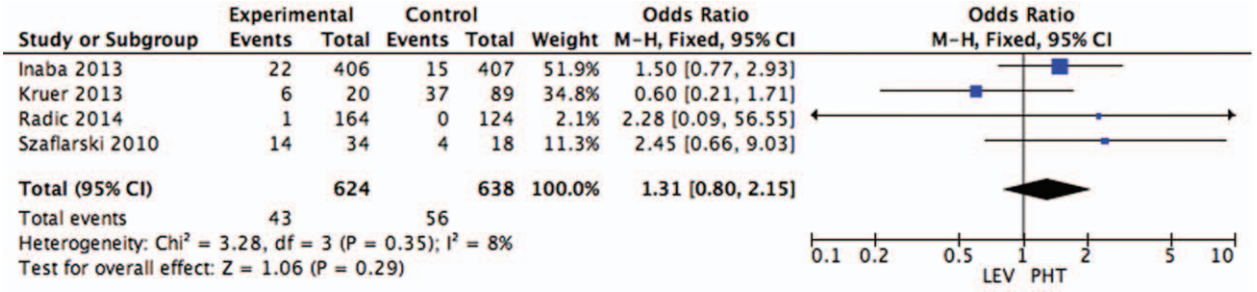

Figure 5. Pooled analysis of mortality between levetiracetam (LEV) therapy and phenytoin (PHT) therapy.

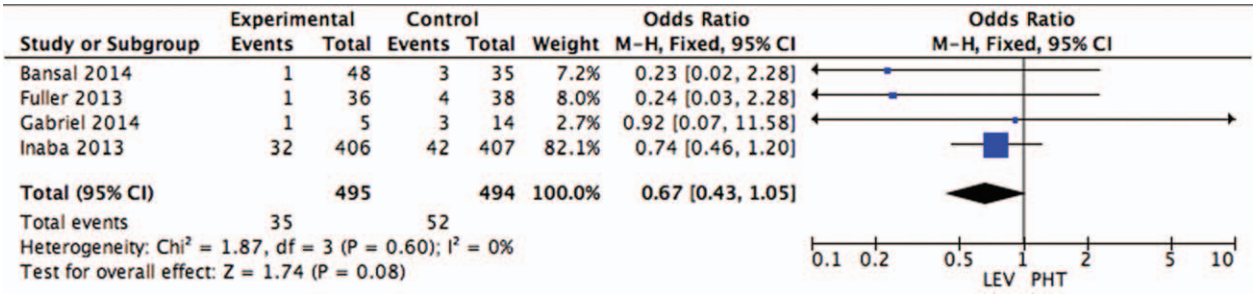

Figure 6. Pooled analysis of side-effects between levetiracetam (LEV) therapy and phenytoin (PHT) therapy.

The PHT has been used for different types of seizures including brain tumors and traumatic BI.[35] The ideal AED for brain tumor patients should be less SEs and will not interfere with drugs commonly used in brain therapy. However, PHT shows controversial results in terms of its effectiveness and the prognostic impact of its adverse reactions, and interferes with the metabolism of many drugs through interaction with the CYP450 enzyme system.[23]

The LEV, the new AED that is devoid of hepatic metabolism, is reported to be well tolerated and at least as effective as PHT.[30] Several studies have reported the efficacy and safety of LEV for seizure prophylaxis.[20,21]

Till now several researchers have compared the efficacy of PHT and LEV to prevent seizures in brain injured patients is still questionable.[20,22] According to our study, there might be significant difference during therapy with LEV in comparison with PHT for early posttraumatic seizure prophylaxis ($P=.04$). These data indicate that LEV may have better efficacy than PHT. This finding may be related to different mechanisms of action, better pharmacokinetic stability, because LEV has only 10% albumin binding, resulting in fewer adverse events leading to treatment interruption.[36,37] In fact, the use of PHT to prevent seizures in patients with hemorrhagic stroke is associated with worse functional outcome.[38] Similar results have been reported in patients with subarachnoid hemorrhage because the use of PHT is associated with poor cognitive status, especially if long-term administration.[39–41]

However, there is no significant difference in terms of overall seizure ($P=.09$), and late seizure ($P=.16$) occurrence. The different treatment choices did impact the occurrence of seizures based on different neurotrauma population, because levels are affected by decreased protein binding, variable gastrointestinal absorption, and increased drug clearance.[26,42] A previous meta-analysis evaluated patients with different BI at increased risk of seizures, including subarachnoid hemorrhage, intraparenchymal hemorrhage, and supratentorial glioma surgery, and compared with those treated with PHT, there is no difference in seizure rates with LEV.[43] These suggested that different BI patients may have a different underlying tendency to seizures and may be associated with different functional outcomes toward the AED.

The use of anticonvulsants may have beneficial effect on preventing posttraumatic seizures. On the contrary, seizure prophylaxis drugs are not without their SEs. In addition to the controversy over the efficacy of LEV and PHT, there are serious SEs related to people.[44] SEs were reported in 4 of the studies and there were no significant differences in terms of SEs. This finding is consistent with previously reported rates of SEs with PHT compared with LEV.[44] The rate of SEs should be a topic of future study and could help to guide the clinician in deciding which agent to use.

There are several potential limitations to this analysis. First, we included patients with different underlying diseases. Due to insufficient data for the included studies, the impact of the subgroup analysis was not assessed. Second, since this study is a research-grade meta-analysis, due to the lack of patient-level data, clinical heterogeneity should be considered when interpreting our findings, and therefore we cannot adjust patient-level confounding factors. Finally, some of these analyses include randomized and nonrandomized clinical trials, which may lead to potential prejudice. Need to clarify more large multicenter randomized controlled trials on efficacy and safety.

5. Conclusion

On the basis of this meta-analysis, patients treated with LEV have similar efficacy to PHT in preventing seizure. To make any

practice recommendations, further high-quality, well-populated studies are necessary to evaluating the safety, functional outcome, and make definitive recommendation(s) on this topic.

Author contributions

Conceptualization: Lin Zhao.
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Investigation: Kai Zhang, Wen-Ling Li.
Methodology: Wen-Ling Li.
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Resources: Jin-Long Qi.
Software: Jin-Long Qi.
Supervision: Jin-Long Qi.
Validation: Yong-Qiang Liu.
Writing – original draft: Lin Zhao.
Writing – review & editing: Yong-Qiang Liu, Kai Zhang.

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