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Original Article

Comparison of levetiracetam versus phenytoin for seizure prophylaxis in patients with traumatic brain injury: A meta-analysis

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Abstract

Introduction: Phenytoin (PHT) is used for seizure prophylaxis in patients with traumatic brain injury (TBI). However, levetiracetam (LEV) is emerging as an alternative. Hence in this study, we aimed to conduct a meta-analysis comparing these two drugs in patients with TBI.

Methods: A systematic search in electronic databases was performed. Studies consistent with our purpose (comparing LEV vs. PHT for the prevention of seizures in TBI patients) were selected for our meta-analysis. We extracted data of all eligible studies on a standard abstraction sheets. Extracted data included patient's demographics, study type, intervention, and outcome. We defined seizures as primary outcome.

Results: 1184 unduplicated papers identified by our search of which 1106 were excluded by reading the abstract and titles. 72 papers were removed by reading the full text. Finally 6 studies (Cohort studies) were selected for analysis. There is no superiority of either these two drugs at preventing of seizures based on the point estimate's odds ratio (OR) = 1.1 [95% confidence interval (CI) = 0.55-2.20].

Conclusion: PHT and LEV showed equal efficacy in prevention of seizures after TBI.

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Introduction

Traumatic brain injury (TBI) is common among individuals 45-year-old or younger and is the leading cause of death in this population.[1] However, there is much morbidity associated with TBI.[1,2] Neurological damage after TBI is often referred to secondary injuries, including post-traumatic seizures (PTS), which has its own sequelae such as hypoxia, increased intracranial pressure, hypoxia, and cardiac arrhythmias.[3-5] These seizures can be classified as early (within 7 days of the injury) or late (more than 7 days after the injury).[6,7]

The incidence of PTS ranges from 2 to 30% for early PTS (≤ 7 days from injury) to 9-42% for late PTS (> 7 days from injury).[3,8,9] Any of the complications mentioned may lead to worsening clinical outcomes.[10,11] Moreover, seizures in this setting could be considered as predictor of the future development of epilepsy. The prevalence of post-traumatic epilepsy is approximately 6% of all epilepsies.[12] In a study done by Annegers et al., up to 11.5% of patients developed epilepsy 5 years after severe civilian TBI.[13] Therefore, high prevalence of post-traumatic epilepsy, the awareness of the

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high incidence of seizures after TBI and contribution of seizures to secondary injuries highlight the importance of preventive anti-epileptic medication by means of prophylactic anti-epileptic drugs (AEDs) in this setting.[12,14-16]

The Brain Trauma Foundation Guideline recommends the use of anticonvulsants for 7 days to prevent early seizures in patients with risk factors associated with PTS (level 2 evidence).[7] These risk factors are the following: Glasgow coma scale (GCS) score < 10, cortical contusion, depressed skull fracture, subdural hematoma, epidural hematoma, intracerebral hematoma, penetrating head wound, seizure within 24 h of the primary injury, and chronic alcoholism.[3,8,17,18] However, administration of prophylactic anticonvulsants is not recommended to prevent late seizures. Several anticonvulsants have been studied to determine whether early use after TBI can reduce the chance of further brain injury and epileptogenesis.[17] Schierhout and Roberts (a Cochrane review study) stated that there is no evidence that prophylactic anticonvulsants use have any influence on mortality or long-term outcomes such as neurological disability, but they decrease incidence of early PTS.[19]

According to the Trauma Brain Foundation Guidelines [endorsed by the American Association of Neurological Surgeons Joint Section on Neurotrauma and Critical Care, the World Health Organization's (WHO) Committee on Neurotrauma, and the Congress of Neurologic Surgeons] anticonvulsants are indicated to decrease the incidence of early PTS. However, early PTS is not associated with worse outcomes.[7]

Conventionally, phenytoin (PHT) has been choice for PTS prophylaxis.[14] Temkin et al. concluded that PHT was effective at prevention of early PTS [relative risk (RR) = 0.33; 95% confidence interval (CI) = 0.19-0.59] and was not effective for late PTS (RR = 0.66; 95% CI = 0.21-2.06).[18] Although PHT is well documented as an effective prophylactic agent in early PTS, it has several rare but high-profile adverse effects such as rash; blood dyscrasias; dermatological events (i.e., Stevens-Johnson Syndrome, epidermal necrolysis); Cytochromes P450 (CYP-450) induction; fever; and hypersensitivity syndrome.[19-24] In addition, PHT requires close serum level monitoring, which is affected by decreased protein binding, variable gastrointestinal absorption, and increased drug clearance, to maintain a narrow therapeutic window.[20,25-27]

Considering these facts, the alternative prophylactic agent should be sought. Valproate could not be a good alternative because it needs serum monitoring as PHT. Besides not only it has similar side effects, but also it increases the mortality rate among valproate-treated PTS patients.[28,29] Carbamazepine as investigated by Glotzner et al., has similar side-effect profiles and also need serum monitoring as PHT dose.[30]

Another alternative for PTS prophylaxis is levetiracetam (LEV). LEV could be a good choice because of its advantages such as fewer side-effect profiles, neuroprotective effects, excellent bioavailability, simpler dosing schedule, and no significant pharmacokinetic interactions.[24,31-34] Two recent studies of cost-effectiveness analysis and cost-minimization analysis both concluded that LEV is less cost-effective than PHT, for PTS prophylaxis.[35,36]

Conflicting outcomes have been reported in the studies comparing LEV and PHT for prophylaxis of PTS. LEV have same early PTS rate as PHT does; however, more abnormal Electroencephalography (EEG) findings were reported in patients treated with LEV versus PHT.[37,38] Although it was reported that LEV is associated with better long-term outcomes,[14] in a recent study, Gabriel and Rowe showed that there is no difference in long-term outcome for patients received LEV or PHT as a PTS prophylaxis.[34] Considering these conflicting results from different studies we aimed to conduct a meta-analysis of previous studies comparing the efficacy of LEV and PHT in patients with TBI.

Methods

A computerized literature search was performed on Medline (1966-2014), Embase (1947-2014), Scopus (1966-2014) and Cochrane (1993-2014) for all comparative studies and conference abstracts for studies comparing prophylactic effect of LEV to PHT

among patients with TBI. We used following keywords including their truncations, abbreviation, synonyms and subsets in our search strategy: PHT (Dilantin), LEV (keppra), seizure (epilepsy), brain (head) injury (TBI, craniotomy) using a combination of medical subject headings (MESH) terms and text words searches for synonyms and related diseases. Several search strategies were constructed to maximize the number of citations generated. Current study followed the guidelines of the meta-analysis of observational studies in epidemiology (MOOSE) group and preferred reporting items for systematic reviews and meta-analysis (PRISMA) criteria.[39]

The title and abstract of all potentially relevant studies were identified for their contents before the retrieval of full articles. Full articles were scrutinized for the relevance if the title and abstract were ambiguous. Furthermore, papers without abstracts but whose titles suggested that they could be related to the objectives of this review were also selected, thus, the full texts could be screened for eligibility. The search ended in November 2014. Two reviewers independently screened all studies and selected articles that satisfied the inclusion criteria; (a) Comparative study (Cohorts, observational studies), (b) The study population consisted of patients with TBI or craniotomy for TBI, (c) The study compared PHT to LEV and (d) The study reported outcomes of seizures and/or side effects. Studies used combination therapies instead of PHT and LEV monotherapy were excluded unless there were separate arms for monotherapy. We aimed to include observational studies. Disagreements were resolved through group discussion with a third author and consensus discussions. On the other hand, non-English were excluded. Case reports, letters, and historical reviews were excluded.

We used a worksheet to retrieve information about all studies that qualified for final inclusion. Data sheets were designed based on previous studies focusing on the similar issue and PRISMA guideline. The extraction was checked by another author independently. Extracted information consists of study characteristics, population characteristics, operational definitions, and outcomes. For missing information needed emails were sent to the corresponding or first author.

Outcome information was collected for seizures. "Early" seizures defined as number of patients that experienced a seizure within a given time interval as defined by the author. If the time intervals varied, we took it to be from injury till discharge or within 30 days. Since there is no consensus on the definition of "early seizures" as seizures occurring within 7 days. We defined "Late seizures" as the number of patients experienced a seizure at 6 months follow-up.

Newcastle-Ottawa scale (NOS) was used to assess the quality of eligible studies. This scale grades each study on three domains; selection (maximum of 4 stars), comparability (maximum of 2 stars) and outcome assessment (maximum of 3 stars).

Primary outcomes were early and late seizures. Meta-analysis was performed on the data when more than one study was available for data. Odds ratio (OR) was used for summary effect estimate with 95% of CI. We used random effects model, and Forest Plots generated. We assessed for statistical heterogeneity using Cochran's Q statistic and the I2 statistic. $P \leq 0.100$ or an I2 value $\geq 50\%$ was considered as evidence of heterogeneity. Publication bias was assessed by the Egger test and visual inspection of the Funnel plot (Figure 1). $P \leq 0.050$ was considered as evidence of significant publication bias. Analyses were performed using comprehensive meta-analysis (CMA) (version 2.26) software.

Results

We identified 1497 studies initially by our search strategy (Figure 2). 313 studies removed for being duplicates. By screening titles and abstracts, 1106 studies were removed, and 78 studies were selected for retrieving the full text. 6 studies from these studies were selected to be eligible for our meta-analysis. We contacted authors for

further information when necessary. We limited our analysis to early and late seizure. 6 studies reported this outcome, were selected for our analysis.[34,37,40-43] All studies had sufficient quality for including in the analysis (Table 1).

Characteristics of the studies are presented in table 2. They are all recent publication from 2008-2014 and were conducted in USA. Total study population was 1523 patients with TBI. Mean age was 47.2 year for patients received PHT and 46.8 year for LEV group. 70.4% of patients in PHT group were male compared to 68.8% in LEV group. Seizure occurrence defined as primary outcome, was assessed at intervals ranged from 7 days to 30 months. In Caballero et al.[42] study continuous EEG monitoring was performed till discharge.

6 studies reported seizures. Studies follow-up intervals ranged from 7 days to 30 months. Considering point estimate no superiority of either drug at preventing early seizures was demonstrated (Figure 3). The point OR was 1.1 (95% CI: 0.55-2.20). Also, no heterogeneity was found. Cochran Q statistic P = 0.488 and the I2 value was 0.001. Publication bias was assessed by the Egger test and visual inspection of the Funnel plot (Figure 1).

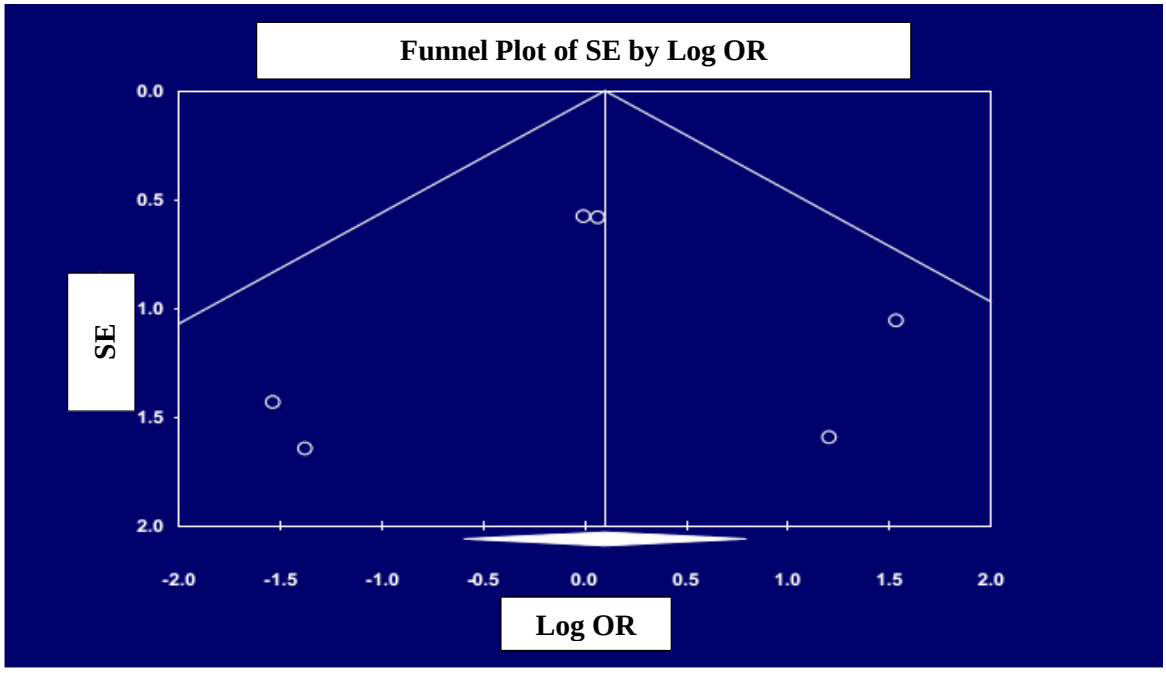

Figure 1. Funnel plot of standard error by log odds ratio
SE: Standard error; OR: Odds ratio

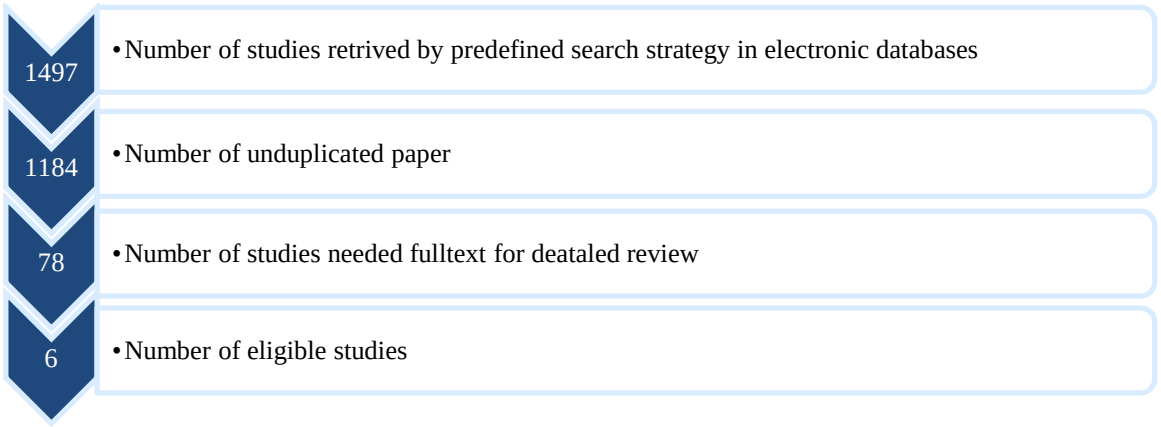

Figure 2. Study selection flow chart

Table 1. Quality assessment of eligible studies

Study	Type	Selection	Comparability	Outcome/exposure
Gabriel and Rowe[34]	Cohort	****	*	***
Jones et al.[37]	Cohort	***		***
Inaba et al.[40]	Cohort	****	**	***
Kruer et al.[41]	Cohort	****	*	***
Caballero et al.[42]	Cohort	****	**	***
Milligan et al.[43]	Cohort	****	*	***

Table 2. Characteristics of eligible studies included in the meta-analysis

Study	Country	Population type	Mean age (years)		Males [n (%)]		Analyzed (patients)		Outcome (seizure)		Seizure assessed at
			PHT	LEV	PHT	LEV	PHT	LEV	PHT	LEV	
Jones et al.[37]	USA	Severe TBI	34.6	33.2	30 (75.0)	23 (73.0)	41	32	0	1	7 days
Milligan et al.[43]	USA	Supratentorial surgery	60.0	56.3	99 (47.0)	41 (39.0)	210	105	9	1	7 days and 900 days
Inaba et al.[40]	USA	Severe TBI	53.6	51.7	280 (68.8)	300 (73.9)	407	406	6	6	990 days
Kruer et al.[41]	USA	Acute TBI	43.1	34.1	76 (85.4)	19 (95.0)	89	20	1	1	7 days and discharge
Caballero et al.[42]	USA	TBI	45.0	57.0	54 (75.0)	14 (77.8)	72	18	21	5	Continuous monitoring till discharge (at least 1 day for 30 min)
Gabriel and Rowe[34]	USA	TBI	46.8	48.8	10 (71.4)	3 (60.0)	14	5	3	0	7 days and 180 days or later

PHT: Phenytoin; LEV: Levetiracetam; TBI: Traumatic brain injury

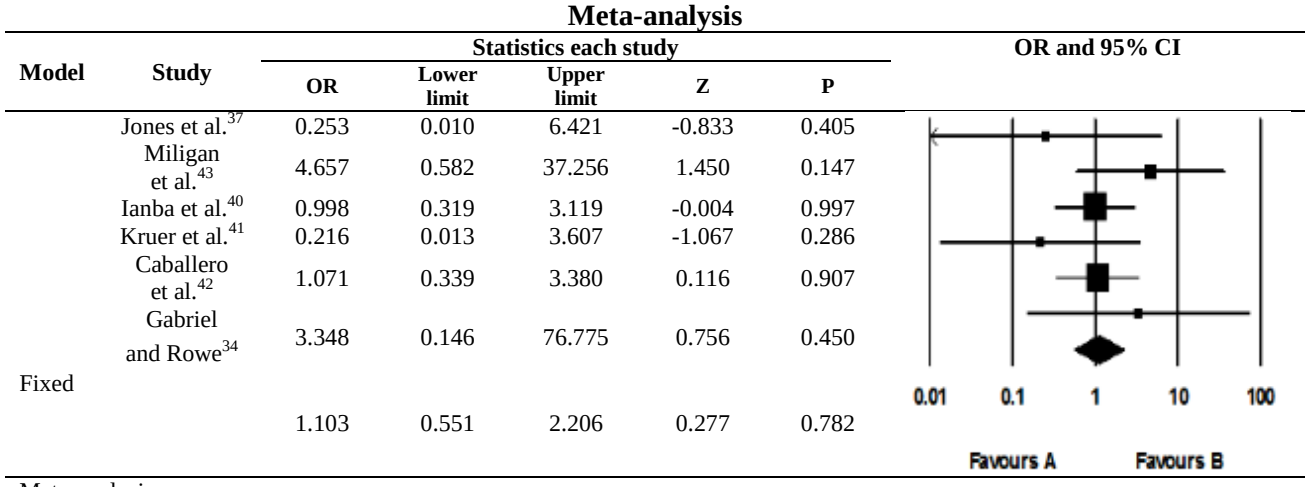

Figure 3. Forrest plot of studies reporting early seizures
OR: Odds ratio; CI: Confidence interval

Discussion

Based on our meta-analysis, we found no significant difference between LEV and PHT in the effectiveness of seizure prophylaxis in patients with TBI. It was consistent with results of previous studies in this filed.[14,44] TBI poses a major health and socioeconomic problem throughout the world today.[45]

A seizure is known as one important complication of TBI. Annegers et al. reported that during the 1st year of post-injury < 1% of patients with mild TBI and 6% of patients with Severe TBI developed seizure.[8] Temkin et al. reported a 2-year seizure rate of 21% in

patients with severe TBI.[15]

Currently, PTS prophylaxis during the first 7 days after TBI is a part of Brain Trauma Foundation Guidelines and is endorsed by American Association of Neurological Surgeons, Congress Neurological Surgeons, and the American Association of Neurological Surgeons-Congress of Neurological Surgeons Joint Section on Neurotrauma and Critical Care. The AED that has been the best choice is PHT.

The effectiveness of PHE in seizure prophylaxis in patients with TBI is well documented and widely accepted.[14,15,18] However, it has its own drawbacks such as side-effects and complication especially on long-term uses.[19-24,28,29,46] Other AEDs such as phenobarbital, carbamazepine, and valproate have been studied for seizure prophylaxis, but no additional benefit was demonstrated with these AEDs.[28,30,47] Recently LEV has been of particular interest. Recent studies on LEV demonstrated that not only it could be a good choice for PTS prophylaxis, but also it has neuroprotective effects.[24,32,33]

Based on our meta-analysis, we found no significant difference between LEV and PHE in the effectiveness of seizure prophylaxis in patients with TBI. It is consistent with results of previous studies in this field.[14,34,40,44] Gabriel and Rowe claimed that patients with TBI treated with LEV was less likely to experience complications during hospitalization than PHE.[34] The same, we found that patient in LEV group experienced fewer complications than those in PHE group did.

In this meta-analysis comparing the efficacy of LEV versus PHT for the prevention of PTS, no superiority of the either drug was seen; however, the rate of complications associated with LEV was less than seen PHE group.

Conclusion

In this meta-analysis of studies evaluating PTS prophylaxis, LEV had no significant superiority to PHE in preventing PTS. However, less complication were seen in a patient treated with LEV than those treated with PHE.

Conflict of Interests

Authors have no conflict of interest.

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