Clinical Research

Comparative efficacy of intravenous levetiracetam and phenytoin in status epilepticus: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

BACKGROUND Status epilepticus (SE) is a neurological emergency, with the current guidelines for second-line anticonvulsants may include phenytoin, levetiracetam, valproic acid, and phenobarbital. However, some studies suggest that levetiracetam may be better at stopping seizures in SE. This study aimed to compare the efficacy of intravenous (IV) levetiracetam and phenytoin in SE.

METHODS We searched PubMed, ScienceDirect, Cochrane, and Google Scholar for randomized controlled trials (RCTs) on administering IV levetiracetam or phenytoin in patients with SE. RCTs were screened using eligibility criteria, and their quality was assessed using the Cochrane risk of bias tool. Heterogeneity was assessed using the I^2 test, and publication bias was evaluated using Egger's test. All analyses were performed using Review Manager version 5.4 (The Cochrane Collaboration, UK) and Stata 17 (StataCorp LLC, USA).

RESULTS 12 RCTs involving 2,137 patients (1,099 receiving levetiracetam) met the inclusion criteria. Pooled analysis showed that levetiracetam therapy had a significantly higher rate of seizure cessation than phenytoin (RR: 1.10, 95% CI = 1.05–1.14, $p = 0.02$, $I^2 = 51\%$). Less adverse events were observed in the levetiracetam group (9.34%) than in the phenytoin group (11.62%; RR: 0.82, 95% CI = 0.66–1.02, $p = 0.07$). However, there was no significant difference regarding IV levetiracetam or phenytoin administration with the incidence of admission to critical care (RR: 1.01; 95% CI = 0.93–1.10, $p = 0.80$) and mortality (RR: 1.08; 95% CI = 0.54–2.15; $p = 0.82$).

CONCLUSIONS IV levetiracetam was significantly better in the cessation of seizures in SE patients than phenytoin.

KEYWORDS levetiracetam, phenytoin, status epilepticus

Status epilepticus (SE) is a neurological emergency characterized by prolonged or recurrent seizures, with an unconscious phase between seizures. Associated morbidity and mortality are high,[1] with an annual incidence of 6–41 per 100,000 individuals. Incidence in the elderly is approximately 3 to 10 times higher than that in young adults.[2] The mortality rate of SE ranges from 9% to 21%, increases with age, and depends on seizure duration, age at seizure onset, and etiology.[3]

SE requires immediate targeted treatment to reduce morbidity and mortality. Various clinical studies on SE treatments have been conducted to stop seizures early and prevent recurrence. Clinical practice guidelines recommend benzodiazepines as first-line treatment for patients with SE. If SE is refractory to benzodiazepines, the current guidelines for second-line anticonvulsants include phenytoin, levetiracetam, valproic acid, and phenobarbital. Each

drug has its advantages and disadvantages depending on the patient's clinical condition. However, there is no conclusive evidence that one choice is superior.[3,4]

Phenytoin is a hydantoin derivative anticonvulsant that inhibits nonspecific sodium channels in synapses. Intravenous (IV) phenytoin is widely used because of its wide availability. However, IV administration of phenytoin can cause adverse events such as prolonged QT interval, arrhythmias, and hypotension. Therefore, cardiac monitoring is required periodically following IV administration of phenytoin.

Levetiracetam, a drug in the pyrrolidine class and a newer anticonvulsant, is an alternative second-line SE treatment. The exact antiepileptic mechanism of levetiracetam is still unclear. However, some studies suggested that levetiracetam acts on synaptic vesicle glycoprotein 2A (SV2A), high-voltage activation calcium channels, and the gamma-aminobutyric acid (GABAergic) system. In several observational studies, levetiracetam is superior to phenytoin.[4] This study aimed to compare the effectiveness of levetiracetam and phenytoin as the second-line treatment for SE.

METHODS

Study protocol

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines[5] and registered in PROSPERO (CRD42022363772).

Study selection

A literature search was conducted using the following databases and search engines: PubMed, ScienceDirect, Cochrane, and Google Scholar from January 1 to October 1, 2022. A combination of Medical Subject Headings was used for the search strategy as the following "levetiracetam" AND "phenytoin" AND "status epilepticus." The inclusion criteria for the population, intervention, outcomes, and study design were as follows: (1) population: patients in all age groups with convulsive SE (focal or generalized) despite first-line antiepileptic drug (e.g., benzodiazepine) administration; (2) intervention: IV levetiracetam, phenytoin, or fosphenytoin; and (3) outcome: the primary outcome was clinical seizure cessation. The secondary outcomes were adverse events, admission to critical care, and all-cause mortality; (4) study design: randomized controlled trials (RCTs).

The included RCTs were required to include the primary outcome but did not require all secondary outcomes. Studies that had not been translated into English or provided the full text were eliminated. Studies using combination therapy with anticoagulants and/or antiplatelet agents were excluded.

Selection of studies

All reference lists from the electronic databases were stored and processed using the Rayyan Systematic Review Tool (Rayyan System Inc., USA). Two authors (GAT and NID) independently assessed the reference lists and screened the titles and abstracts. Duplicate and ineligible studies were also excluded. Two authors (GAT and NID) independently obtained full-text articles from relevant studies for further screening. Any disagreements during this process were resolved by discussion with a third author (FHFR or VKR), as needed.

Data extraction

GAT and NID extracted data on study characteristics, interventions, and outcome details. The baseline characteristics included the main study characteristics (first author, year of publication, study design, country of study, number of included patients, age, sex, and history of previous seizures) and quantitative outcomes (clinical seizure termination, adverse events, critical care admission, and death). GAT, NID, and FHFR developed a data extraction form (Microsoft Excel; Microsoft, USA) for data collection.

Data synthesis

Statistical analyses were performed using the Review Manager 5.4 (The Cochrane Collaboration, UK) and Stata 17 (StataCorp LLC, USA). The risk ratio (RR) and 95% confidence interval (CI) were analyzed using dichotomous outcomes and calculated using a fixed-effects model. Heterogeneity was estimated using the I^2 test, with $I^2 > 50\%$ indicating substantial heterogeneity. A two-sided test was performed for all analyses, with a p-value of <0.05 considered statistically significant.

Risk of bias assessment

GAT and NID independently assessed the eligibility criteria and study quality using the Cochrane risk of bias tool (Center for Evidence-Based Medicine Odense and Cochrane Denmark, Denmark) under five domains

(sequence generation, allocation concealment, blinding, detection bias, and attrition bias). Each domain was assessed as low, unclear, or high risk. Any disagreements during this process were resolved by discussion with a third author (FHFR). Egger's test was performed to statistically analyze possible publication bias.

RESULTS

Study selection result

A total of 467 records were obtained during the initial search. After removing duplicates, the titles and abstracts of 376 records were screened. Eighteen articles were assessed for feasibility, and only 12
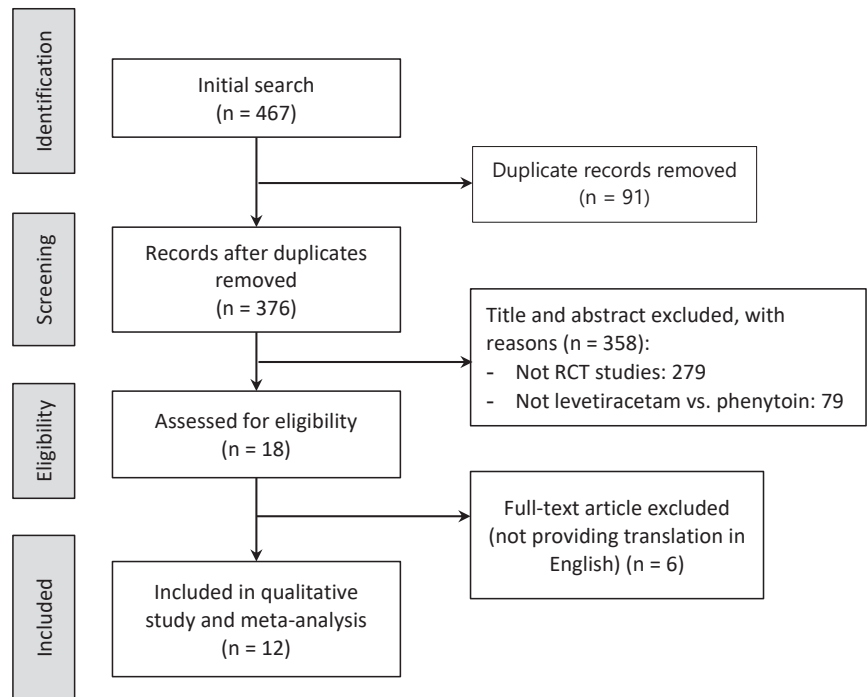

Figure 1. Searching strategy

Table 1. Summary of the studies

First author, year	Country	Ratio M:F (n)	Drug dosage (mg/kg)		Age (years), mean (SD)		History of previous seizure (n)		SE treatment (n)		Seizure cessation (n)	
			LEV	FEN	LEV	FEN	LEV	FEN	LEV	FEN	LEV	FEN
Appleton,[6] 2020	UK	147:139	40	20	3.15 (0.87)	3.15 (0.75)	83	85	152	134	106	86
Chakravarthi,[7] 2015	India	27:17	20	20	39.00 (18.40)	31.82 (12.68)	17	14	22	22	13	15
Chamberlain,[8] 2020	USA	180:137	60	20	28.6 (25.9)	28.2 (25.3)	112	97	175	142	82	66
Dalziel,[9] 2019	Australia and New Zealand	112:121	40	20	3.8 (1.25)	4.0 (1.5)	54	55	119	114	61	62
Gujjar,[10] 2017	Oman	34:18	30	20	38 (19)	37 (19)	NA	NA	22	30	18	22
Mundlamuri,[11] 2015	India	60:40	25	29	34.78 (13.64)	33.24 (13.39)	33	25	50	50	39	34
Nakamura,[12] 2023	Japan	118:58	1–3*	22.5	67 (16)	65 (19)	NA	NA	93	80	83	67
Nalisetty,[13] 2020	India	32:29	40	20	2.74 (2.6)†	2.74 (3.1)†	9	6	32	29	30	20
Nazir,[14] 2020	India	71:29	25	20	4.98 (4.14)	5.17 (3.71)	NA	NA	50	50	39	44
Noureen,[15] 2019	Pakistan	406:194	40	20	3.52 (0.24)	3.46 (0.22)	NA	NA	300	300	278	250
Vignesh,[16] 2020	India	37:30	20	20	58 (50)†	44 (43)†	NA	NA	32	35	30	31
Wani,[17] 2019	India	66:38	40	20	3.39 (3.32)	4.80 (4.11)	8	10	52	52	50	31

F=female; FEN=phenytoin; LEV=leviteracetam; M=male; NA=not available; SD=standard deviation; SE=status epilepticus
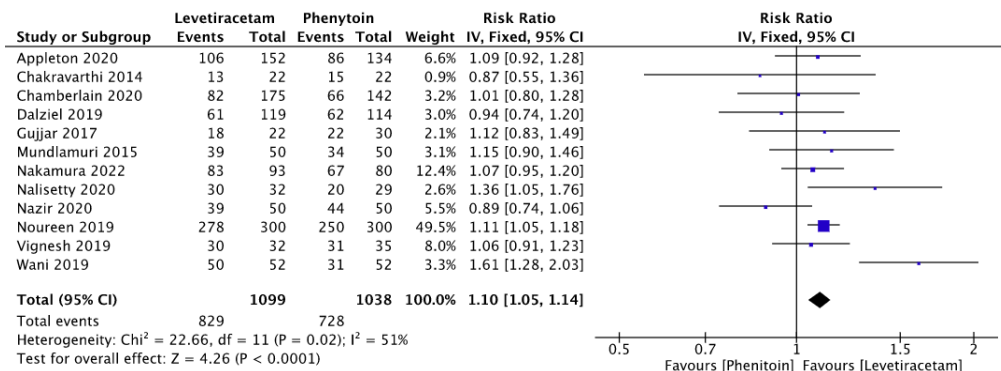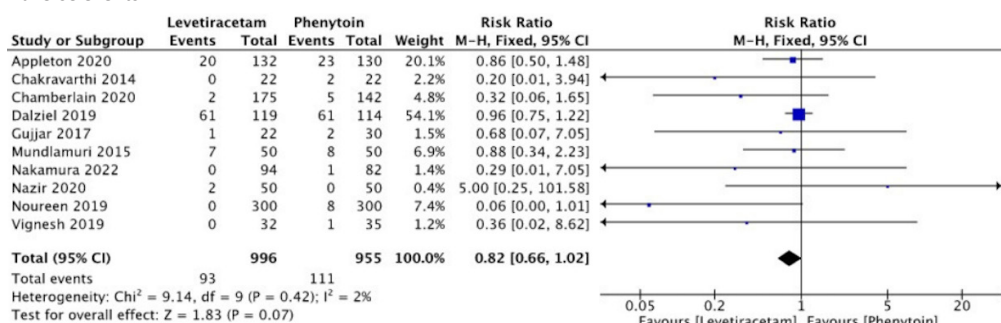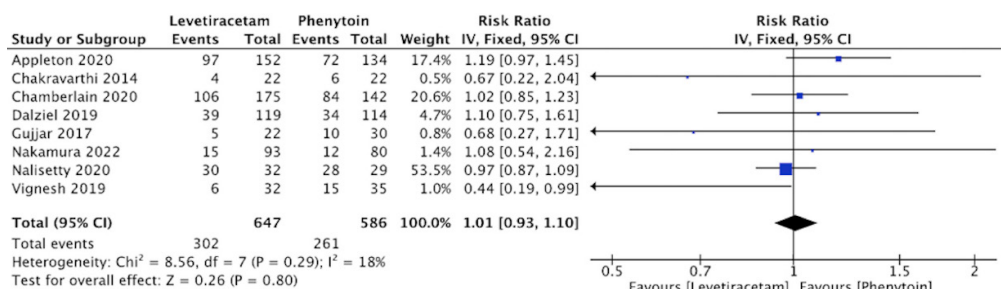*In grams (single dose); †in months

Figure 2. Forest plot of seizure cessation after levetiracetam or phenytoin treatment
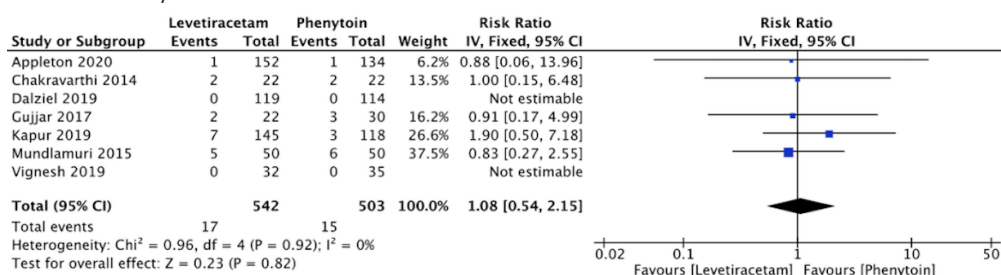

Figure 3. Forest plot of secondary outcomes in status epilepticus after levetiracetam and phenytoin treatment

studies[6–17] that met the criteria were included in the quantitative synthesis (Figure 1).

Clinical characteristics and demography of the included studies

The main characteristics of the studies are summarized in Table 1. In this study, most patients were males (59.1%). Patients' ages ranged from 2.74 (2.6) months to 67 (16) years for the levetiracetam group and 2.74 (3.1) months to 65 (19) years for the phenytoin group. In 12 clinical studies, 2,137 patients with SE were randomized to receive IV levetiracetam (1,099 patients) or phenytoin (1,038 patients). A total of 608 (53.1%) patients had a history of seizures.

Primary outcome

Of the 1,099 patients who received IV levetiracetam, seizures stopped in 829 (75.4%) patients. Seizure cessation was observed in 727 (70.0%) patients who received IV phenytoin. Pooled analysis showed a significant effect of levetiracetam therapy administration on seizure cessation, compared with phenytoin, in patients with SE (RR: 1.10, 95% CI = 1.05–1.14, and p = 0.02 with Z-score = 4.26) (Figure 2).

Secondary outcomes

The secondary outcomes evaluated were adverse events, the need for critical care, and all-cause death in patients with SE after administration of levetiracetam or phenytoin treatment. Approximately 9.34% of the adverse events occurred in the levetiracetam group, which was lower than that in the phenytoin group (11.62%) (Figure 3a). The administration of levetiracetam or phenytoin therapy did not significantly affect critical care needs (Figure 3b) or deaths (Figure 3c).

Risk of bias

Details of the risk of bias assessment are shown in Supplementary Figure 1. Most studies are sufficient to generate random sequences and selective reporting and are at a low risk of bias for incomplete outcome data. Approximately three-quarters of the included studies lacked blinding and were at high risk of performance and detection bias. Half of the studies had low risk of allocation concealment and other possible biases. Quantitative analysis using Egger's test in these 12 studies showed a p-value of 0.12, indicating no evidence of publication bias.

DISCUSSION

The efficacy of levetiracetam and phenytoin as secondary treatments for SE remains controversial. In line with Shi et al[18] and Xue et al,[19] this meta-analysis showed better efficacy of levetiracetam for seizure cessation than phenytoin (RR: 1.12 and 1.14, respectively). In contrast, meta-analyses conducted by Li et al[20] and Feng et al[21] showed that levetiracetam and phenytoin are as effective in SE seizure cessation. In addition, there was no significant difference in critical care admissions between the levetiracetam and phenytoin groups. Li et al[20] only included seven RCTs and did not include the RCT by Chamberlain et al[8] which was a multicenter study with a large sample

size. The most recent RCT by Nakamura et al[12] in 2022 was not included from the meta-analysis by Feng et al[21]. Furthermore, the number of studies included in this review was greater than that in previous studies (1,028 *versus* 2,137).[20] Additional RCT will increase the sample size of this study, thus making it possible to obtain more accurate and convincing results.

There was no significant difference in the incidence of critical care admission and mortality between patients receiving IV levetiracetam and phenytoin. Several factors can affect admission to critical care and mortality, in addition to the adverse effects of drugs. SE can have long-term consequences, including nerve death, nerve injury, and changes in the nerve tissue, depending on the type and duration of the seizure. In addition, the presence of metabolic diseases, infections, and prolonged seizures can affect mortality in SE.[22]

Most of the included studies used the same dosage of IV phenytoin, while the dosage of IV levetiracetam varied from 20 to 60 mg/kg. This difference was due to the different guidelines for IV levetiracetam dosing in each country.[23] The present study showed a higher percentage of adverse events in the phenytoin group. Although phenytoin has been the antiepileptic drug of choice for several decades, it has several side effects including hypotension, cardiac arrhythmias, gingival hyperplasia, megaloblastic anemia, sedation, and hirsutism. Phenytoin acts on the sodium channels of the synapses by reducing the influx of sodium across nerve membranes and limiting the release of action potentials and overexcitation, which can lead to seizures. It is metabolized in the liver by cytochrome P450 (CYP450) enzymes, resulting in interactions with other drugs metabolized by CYP450, such as warfarin.[4]

The mechanism of action of levetiracetam is still not clearly understood; however, a recent study suggested that it inhibits neurotransmission by binding to SV2A in all synapses and decreases excitatory transmission by blocking the high-voltage-activated calcium channels (N-type, L-type, and P/Q-type calcium channels) of hippocampal pyramidal neurons.[4,24] It also works on the GABAergic system in the central nervous system. However, the results are still conflicting.[24] Although levetiracetam has no known serious adverse events in the organ system, the most common side effects are drowsiness, dizziness, headache, fever, dry mouth, asthenia, and behavioral changes. Acute thrombocytopenia and eosinophilia

are hematological adverse effects of levetiracetam, which often occur in SE patients.[24–26] No relevant pharmacokinetic interactions were found between levetiracetam and other antiepileptic drugs. In addition, levetiracetam does not interact with digoxin, warfarin, or low-dose contraceptive pills; however, an adverse pharmacodynamic interaction was found between levetiracetam, carbamazepine, and topiramate.[27]

This study provides high-quality evidence supporting the use of IV levetiracetam over phenytoin for treating SE. However, this meta-analysis had several limitations. Although all the studies were RCTs, most were open trials. In addition, different doses and infusion times of therapy across the studies might have caused potential bias, affecting the results. IV levetiracetam is not widely used in Indonesia, both in studies and clinical practice for managing SE, as the Indonesian Neurologist Association (PERDOSSI) guidelines recommend oral levetiracetam. Therefore, further studies are needed to compare the route of administration (oral and IV) and to determine the optimal dosage of levetiracetam for the treatment of SE.

In conclusion, IV levetiracetam was superior to IV phenytoin for seizure cessation. Moreover, a lower incidence of adverse events was observed with IV levetiracetam. No significant difference was found between IV levetiracetam or phenytoin administration with respect to the incidence of admission to critical care and all-cause deaths.

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