Mini Review Article

Phenytoin versus other antiepileptic drugs as treatments for status epilepticus in adults: a systematic review and meta-analysis

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Aim: Status epilepticus (SE) is a life-threatening neurological emergency. There is insufficient evidence regarding which antiepileptic therapy is most effective in patients with benzodiazepine-refractory convulsive SE. Therefore, this study aimed to evaluate intravenous phenytoin (PHT) and other intravenous antiepileptic medications for SE.

Methods: We searched PubMed, the Cochrane Central Register of Controlled Trials, and Igaku Chuo Zasshi for published randomized controlled trials (RCTs) in humans up to August 2019. We compared outcomes between intravenous PHT and other intravenous medications. The important primary composite outcomes were the successful clinical cessation of seizures, mortality, and neurological outcomes at discharge. The reliability of the level of evidence for each outcome was compared using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Results: A total of 1,103 studies were identified from the databases, and 10 RCTs were included in the analysis. The ratio of successful clinical seizure cessation was significantly lower (risk ratio [RR] 0.89; 95% confidence interval [CI], 0.82–0.97) for patients treated with intravenous PHT than with other medications. When we compared mortality and neurological outcomes at discharge, we observed no significant differences between patients treated with PHT and those treated with other medications. The RRs were 1.07 (95% CI, 0.55–2.08) and 0.91 (95% CI, 0.72–1.15) for mortality and neurological outcomes at discharge, respectively.

Conclusions: Our findings showed that intravenous PHT was significantly inferior to other medications in terms of the cessation of seizures. No significant differences were observed in mortality or neurological outcomes between PHT and other medications.

Key words: Neurological outcome, phenytoin, seizure cessation, status epilepticus

INTRODUCTION

Status epilepticus (SE) is a major medical emergency associated with significant neurological outcomes and mortality. The current definition of SE is 5 min or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures.[1-3] Convulsive SE is defined as an acute epileptic condition characterized by continuous generalized convulsive seizures for at

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least 5 min or two seizures without full recovery of consciousness between seizures.[1-3] The adverse effects of SE include both indirect systemic problems arising from the convulsive state and direct neuronal injury.[3] Most evidence supports the use of benzodiazepines as the initial treatment for SE.[4-6] The American Epilepsy Society published a set of guidelines in which they recommended the intravenous (i.v.) administration of phenytoin (PHT), valproate (VPA), levetiracetam (LEV), or phenobarbital (PB) as the treatment for refractory convulsive SE.[7] However, evidence regarding which drug is most effective in patients with benzodiazepine-refractory convulsive SE is insufficient. Additionally, in a survey of critical care neurologists published in 2003, 95% of responders (n = 106) used fosphenytoin or PHT for the treatment of established SE.[8] Thus, PHT is the oldest and most used drug for this purpose; but with the recent launch of new drugs, its effectiveness should be reexamined.

Research question

Which antiepileptic drugs (AEDs)—phenytoin or other medications—should be used in adult patients with benzodiazepine-refractory convulsive SE?

We identified randomized controlled trials (RCTs) for inclusion based on the research question and according to the PICO (participants, interventions, comparisons, and outcomes) criteria: participants, adults (≥15 years old) with SE; interventions, administration of drugs to treat SE in prehospital, emergency room settings; comparisons, administration of other antiepileptic medications; and outcomes, the primary outcomes were seizure cessation, mortality, and good neurological outcomes.

METHODS

In 2020, the Japan Resuscitation Council (JRC) Neuroresuscitation Task Force and the Guidelines Editorial Committee were established. The JRC Neuroresuscitation Task Force established six clinically relevant questions, and this systematic review was carried out based on these questions.

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[9,10] we undertook a systematic review and meta-analysis. This study was registered in the University Hospital Medical Information Network (UMIN) of the National University Hospital Association, Japan (https://www.umin.ac.jp registration no. R000045525UMIN000039934). As this study was a systematic review with a meta-analysis, ethics committee approval was not required.

Search strategies

Databases such as MEDLINE (through PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and Igaku Chuo Zasshi (ICHUSHI) were searched to retrieve relevant articles for the review. We searched for full-text RCTs carried out in humans published until August 2019. We used a combination of key terms and established a full search strategy (File S1).

Study selection and inclusion criteria

The study population of interest consisted of patients in settings ranging from prehospitalization to the emergency room who were suspected to have benzodiazepine-refractory convulsive SE. We did not restrict our analysis by country and included all severities and types of SE. Conference abstracts and animal studies were excluded. We only included studies that were written in English or Japanese.

We compared the outcomes between PHT and other medications. The critical outcomes in the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system were the successful clinical termination of seizures, mortality at discharge, and neurological outcome at discharge, as assessed by the functional independence measure (FIM; a good outcome was a FIM score ranging from 5 to 7, and a poor outcome was a score ranging from 1 to 4) or the modified Rankin Score (mRS; a good outcome was an mRS score ranging from 0 to 3, and a poor outcome was a score ranging from 4 to 6).

Data extraction and management

Two independent reviewers (EH and MU) screened the titles and summaries of the study and then reviewed the relevant full-text articles.

Disagreements were reviewed until an agreement was reached. The two reviewers individually reviewed the full text of the articles included in the final selection. Disagreements were resolved by a third reviewer (JK). The flow diagram of our study, which was adapted from the PRISMA statement (2009),[10] is shown in Fig. 1.

Meta-analysis

We undertook a meta-analysis because sufficient data were available according to the "Cochrane Handbook for Systematic Reviews of Interventions" and PRISMA guidelines. The results were summarized using a random effects model to facilitate the pooling of treatment effect estimates. Risk

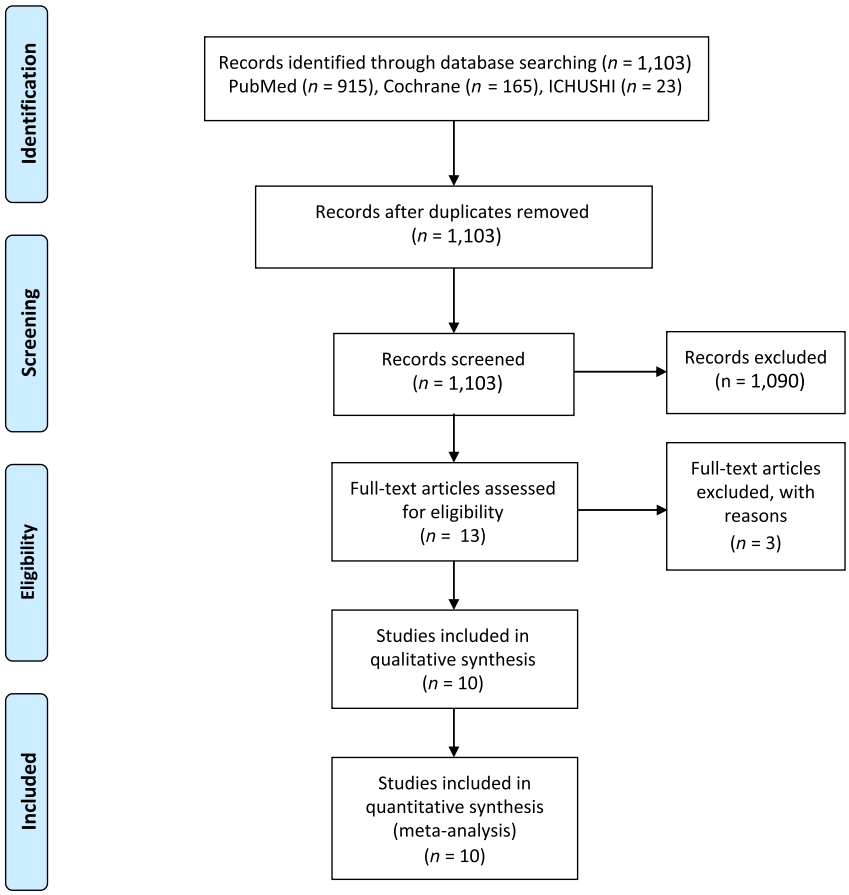

Fig 1. Flowchart of the study selection process to compare phenytoin and other antiepileptic drugs as treatments for status epilepticus in adults.

ratios (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous outcomes.

Heterogeneity between trials for each outcome was evaluated using the I^2 statistic.[11] Heterogeneity was determined by calculating I^2 values, which were interpreted as follows: 0–40%, might not be important; 30–60%, may represent moderate heterogeneity; 50–90%, may represent substantial heterogeneity; and 75–100%, considerable heterogeneity. Quantification of heterogeneity is only one component of a wider investigation of variability across studies, the most important being diversity in clinical and methodological aspects. Meta-analysts must also consider the clinical implications of the observed degree of inconsistency across studies.[12,13] A funnel plot was generated to investigate the potential for publication bias. Estimates were pooled using a random effects model. The meta-analysis was undertaken based on all published data and data made available by the authors of the original studies.

Subgroup analysis

We compared the outcomes between PHT and other medications. However, because other drugs contain many types of drugs, we compared PHT directly with each drug in regard to seizure cessation. Of the 10 RCTs, only four studies investigated mortality, and only two studies investigated neurological outcomes. Therefore, we did not undertake subgroup analyses of these parameters.

Risk of bias assessment

The Cochrane and GRADE system risk of bias tools were adopted to assess the quality of the included studies.[14] Each study was assessed for: (i) random sequence generation (selection bias), (ii) allocation concealment (selection bias), (iii) the blinding of participants and personnel (performance bias), (iv) the blinding of related outcome

assessments (detection bias), (v) incomplete outcome data (attrition bias), (vi) selective reporting (reporting bias), (vii) other sources of bias. Studies were categorized as having a low, unclear, or high risk of bias in each domain. The risk of bias for each element was considered "high" when bias was present and likely to affect the outcomes and "low" when bias was absent or present but unlikely to affect the outcomes.[15]

Two independent reviewers (EH and MU), chosen from among the authors, carried out the risk of bias assessments. Disagreements were resolved through discussion.

Rating the certainty of evidence using the GRADE approach

We used the GRADE tool to rate the quality of the evidence for the effect of i.v. PHT and other medications on adult patients with SE.[16-19] The certainty of the evidence was assessed as high, moderate, low, or very low based on the evaluation of the risk of bias, inconsistency, indirectness, imprecision, and publication bias. We generated an evidence profile table using GRADEpro GDT (GRADEpro Guideline Development Tool software developed by Evidence Prime, available from https://gradepro.org). We received guidance regarding the use of the GRADE system from the Medical Information Network Distribution Service (MINDS), a Japanese educational center for the GRADE system. Two reviewers also discussed the results of the risk of bias assessment and achieved a consensus on the final determination.

We used Review Manager software (Cochrane systematic review software, version 5.3.5; The Nordic Cochrane Centre) to undertake the statistical analysis.

RESULTS

Search of published works

We identi fied 1,103 studies from the electronic databases, and 1,090 studies were excluded because they were not RCTs. Finally, the full texts of 13 studies were reviewed, and 10 studies[20-29] were included in the final analysis (Fig. 1).

Study characteristics

The 10 RCTs[20-29] included 1,012 patients: 485 were assigned to the PHT group and 527 were assigned to the VPA, LEV, or PB group. The definition of SE was different in each RCT. No RCTs carried out in Japan compared the effect of i.v. PHT and other i.v. antiepileptic medications on the treatment of adults with SE as a second-line treatment. The individual characteristics of the trials included in this meta-analysis are shown in Table 1. The risk of bias was evaluated for each study, and the results are shown in the risk of bias summary in Fig. 2A–C (green [+], low risk; red [−], high risk).

Outcomes

The pooled RR for the cessation of seizures (10 RCTs, n = 1,012) (20-29) was statistically significant (RR 0.89; 95% CI, 0.82–0.97) (Fig. 3A), showing the superior effect of other medications compared to PHT. However, due to the overlap of other drugs, we compared PHT directly with each drug for effects on seizure cessation.

Therefore, we undertook the following subgroup analyses of seizure cessation. When performing pairwise comparisons of PHT and VPA, LEV, or PB, no significant differences were observed between PHT and the other medications. The pooled RRs were 0.91 (95% CI, 0.82–1.01), 1.00 (95% CI, 0.84–1.19), and 0.94 (95% CI, 0.75–1.18) for the comparison of seizure cessation induced by PHT and VPA (Fig. 4A), PHT and LEV (Fig. 4B), and PHT and PB (Fig. 4C), respectively.

Two hundred ninety-eight patients (four RCTs, n = 298) died: 149 had received PHT, and 149 had received other drugs (Fig. 3B). No significant differences were observed in mortality between PHT and the other medications (RR 1.07; 95% CI, 0.55–2.08).

No statistically significant relationship was found between drug choice and good neurological outcomes (two RCTs, n = 96) (RR 0.91; 95% CI, 0.72 to 1.15) (Fig. 3C).

Certainty of evidence

We have summarized the certainty of evidence in the evidence profile table (Table 2).

The certainty of evidence was rated as very low due to the serious risk of bias and indirectness and very serious imprecision with regard to mortality. The certainty of evidence for a good neurological outcome was very low because of the serious risk of bias, indirectness, and imprecision. The certainty of evidence for seizure cessation was low due to the serious risk of bias and indirectness. The overall certainty of the evidence was very low. No statistically significant heterogeneity in mortality or a good neurological outcome was observed between i.v. PHT and other i.v. medications (I^2 = 0%, χ^2 = 0.19, p = 0.98; I^2 = 0%, χ^2 = 0.86, p = 0.35, respectively). Statistically significant heterogeneity was not observed for seizure cessation between PHT and VPA or LEV

Table 1. Baseline characteristics of eligible studies on drug treatments for status epilepticus (SE) in adults

First author, year (country)	Definition of SE and inclusion criteria	Underlying etiology	No. of patients	Duration of SE	Interventions	Outcomes	Notes
Agarwal, 2007 (India)	Continuous or repeated seizure activity >5 min without recovery of consciousness	Reported	VPA 50 PHT 50	VPA <2 h 60%, >2 h 40% PHT <2 h 52%, >2 h 48%	VPA 20 mg/kg i.v. PHT 20 mg/kg i.v. in hospital	Mortality Seizure control Adverse effects	DZP was given in doses of 0.2 mg/kg at 2 mg/min up to a maximum of 20 mg
Amiri-Nikpour, 2018 (Iran)	Continuous generalized convulsive seizure lasting >5 min or two or more discrete seizures during which the patient did not return to baseline consciousness	Reported	VPA 55 PHT 55	NR	VPA 30 mg/kg i.v. PHT 20 mg/kg i.v. in hospital	Mortality Seizure control Adverse effects	DZP was given in doses of 0.2 mg/kg at 2 mg/min up to a maximum of 20 mg
Chakravarthi, 2015 (India)	Continuous generalized convulsive seizure lasting >5 min or two or more discrete seizures during which the patient did not return to baseline consciousness	Reported	PHT 22 LEV 22	PHT 72.05 ± 48.57 (min) LEV 55.91 ± 73.75 (min)	PHT 20 mg/kg i.v. LEV 20 mg/kg i.v. in hospital	Mortality Seizure control Adverse effects Neurological outcome	LZP was given in doses of 0.1 mg/kg at 1 mg/min
Chitsaz, 2013 (Iran)	Continuous generalized convulsive seizure lasting for approximately 5–20 min or no intervals of consciousness evident between the seizures	NR	VPA 15 PHT 15	NR	VPA 20 mg/kg i.v. PHT 20 mg/kg i.v. in hospital	Seizure control	DZP was given in doses of 0.15 mg/kg at 5 mg/min

Table 1. (Continued)

First author, year (country)	Definition of SE and inclusion criteria	Underlying etiology	No. of patients	Duration of SE	Interventions	Outcomes	Notes
Gilad, 2008 (Israel)	Continued seizure activity for >30 min or two or more sequential seizures without full recovery between seizures	Reported	VPA 18 PHT 9	NR	VPA 30 mg/kg i.v. PHT 18 mg/kg i.v. in hospital	Seizure control Adverse effects	LZP (0.1 mg/kg)
Gujjar, 2017 (Oman)	Prolonged (>5 min) or recurrent generalized tonic–clonic seizure(s) with no return of consciousness between attacks or partial seizures persisting for more than 10 min	Reported	LEV 22 PHT 30	NR	LEV 30 mg/kg i.v. PHT 20 mg/kg i.v. in hospital	Mortality Seizure control Adverse effects Neurological outcome	LZP 4 mg or DZP 5–10 mg over 2 min
Misra, 2006 (India)	Two or more convulsive seizures without full recovery of consciousness between the seizures or continuous convulsive seizures lasting >10 min	Reported	VPA 35 PHT 33	VPA 1.76 ± 0.49 h PHT 1.70 ± 0.47 h	VPA 30 mg/kg i.v. PHT 18 mg/kg i.v. in hospital	Seizure control Adverse effects	
Mundlamuri, 2015 (India)	Continuous generalized seizures lasting ≥10 min or two or more discrete seizures without complete recovery of consciousness in between	Reported	PHT 50 VPA 50 LEV 50	PHT 6.7 ± 6.53 h VPA 7.38 ± 8.39 h LEV 10.18 ± 9.33 h	PHT 20 mg/kg i.v. VPA 30 mg/kg i.v. LEV 25 mg/kg i.v. in hospital	Mortality Seizure control	LZP (0.1 mg/kg; 4–6 mg i.v.) was given within 5 min of arrival

Table 1. (Continued)

First author, year (country)	Definition of SE and inclusion criteria	Underlying etiology	No. of patients	Duration of SE	Interventions	Outcomes	Notes
Shaner, 1988 (USA)	History of 30 min of continuous generalized convulsive seizures and witnessed generalized seizures	Reported	PHT 18 PB 18	NR	PHT 18 mg/kg i.v. PB 10 mg/kg i.v. in hospital	Seizure control Adverse effects	DZP was infused at 2 mg/min i.v. only in the PHT group
Treiman, 1998 (USA)	Two or more generalized convulsions without full recovery of consciousness between seizures or continuous convulsive activity for more than 10 min	Reported	LZP 100 PB 92 PHT 203	NR	LZP 0.1 mg/kg i.v. PB 15 mg/kg i.v. DZP/PHT 0.15 and 18 mg/kg i.v. PHT 18 mg/kg i.v.	Seizure control Adverse effects	

Abbreviations: DZP, diazepam; LEV, levetiracetam; LZP, lorazepam; NR, not reported; PB, phenobarbital; PHT, phenytoin; VPA, valproate.

Fig 2. Risk of bias summary of the included studies comparing phenytoin and other antiepileptic drugs as treatments for status epilepticus in adults. A, Seizure cessation. B, Mortality. C, Good neurological outcome.

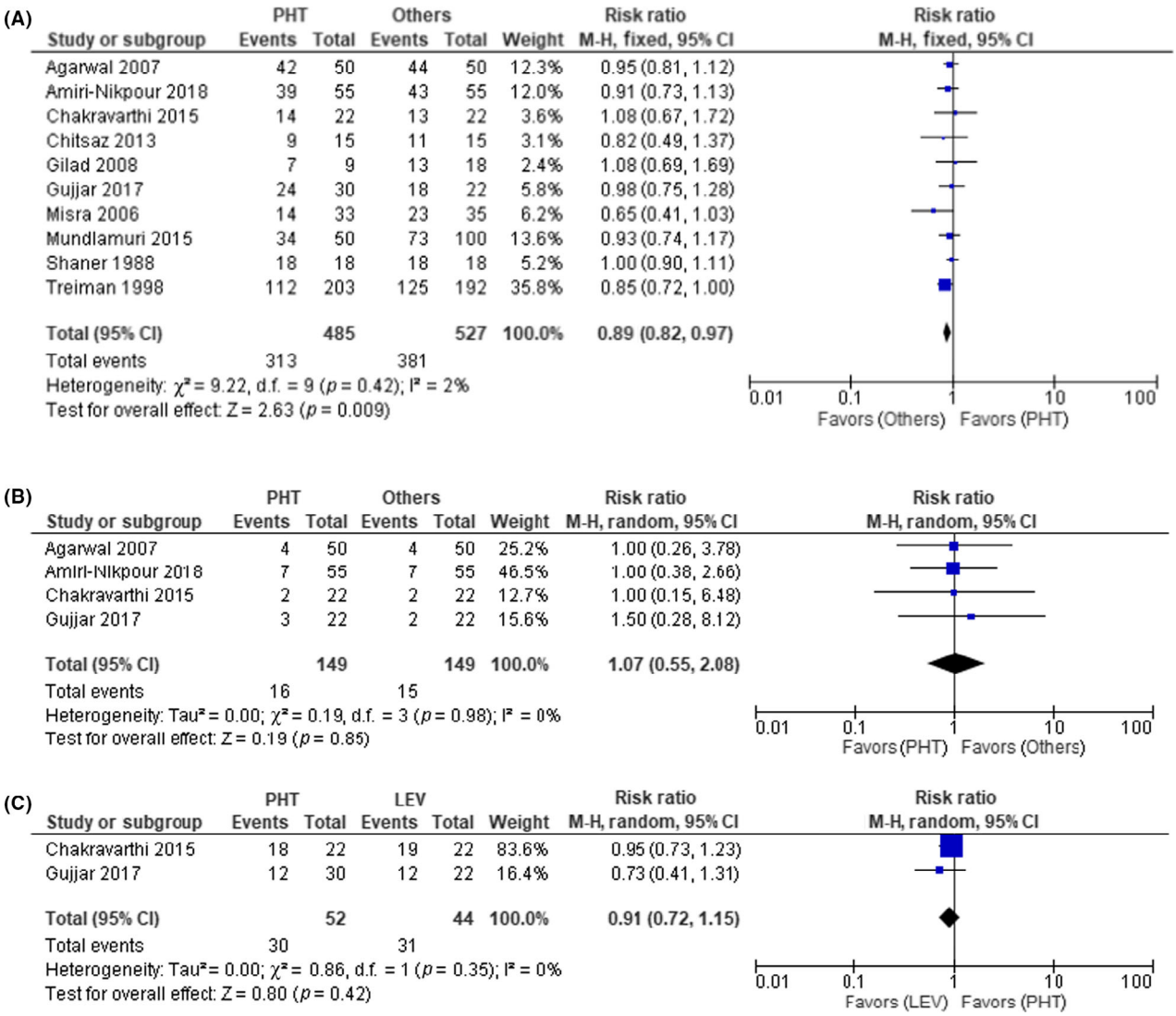

Fig 3. Forest plots of the comparisons of studies comparing phenytoin and other antiepileptic drugs as treatments for status epilepticus in adults. A, Seizure cessation. B, Mortality. C, Good neurological outcome. CI, confidence interval; M-H, Mantel–Haenszel method.

(I^2 = 0%, χ^2 = 3.66, p = 0.60; I^2 = 0%, χ^2 = 0.13, p = 0.94, respectively). However, a comparison of PHT and PB revealed significant heterogeneity (I^2 = 76%, χ^2 = 4.08, p = 0.04).

Publication bias

We assessed publication bias for each outcome by constructing a funnel plot. A visual inspection of the funnel plots suggested no publication bias was observed for mortality, a good neurological outcome, or the cessation of seizures (see Fig. S1).

DISCUSSION

Summary of results

This systematic review evaluated the evidence from RCTs comparing outcomes between i.v. PHT and other i.v. antiepileptic medications (VPA, LEV, and PB) given to adult patients receiving second-line treatment for benzodiazepine-refractory convulsive SE. The 10 RCTs retrieved in this study were published from 1988 to 2018[20-29] and carried out in hospital settings. Phenytoin was significantly inferior to other medications in terms of the cessation of seizures.

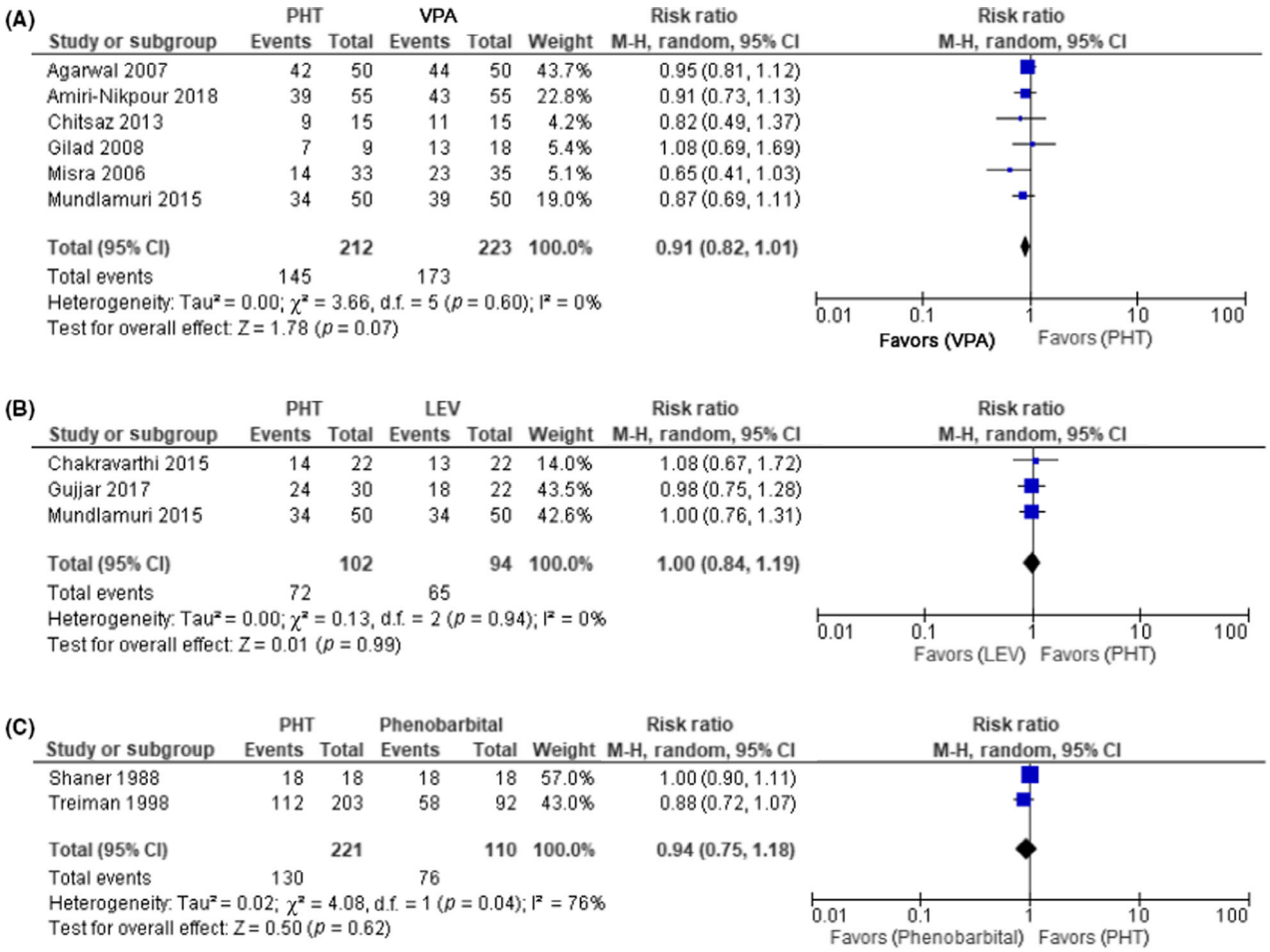

Fig 4. Forest plots of the comparisons of studies comparing phenytoin and other antiepileptic drugs as treatments for status epilepticus in adults (subgroup analyses for seizure cessation). A, Phenytoin versus valproate for seizure cessation. B, Phenytoin versus levetiracetam for seizure cessation. C, Phenytoin versus phenobarbital for seizure cessation. CI, confidence interval; M-H, Mantel–Haenszel method.

Therefore, we subsequently undertook subgroup analyses for seizure cessation using pairwise comparisons of PHT and VPA, LEV, or PB. No significant differences in the effects of PHT versus VPA, PHT versus LEV, or PHT versus PB were observed ($p = 0.07$, $p = 0.99$, and $p = 0.62$, respectively) (Fig. 4). No statistically significant difference was found regarding mortality or good neurological outcomes. However, significant heterogeneity was observed in the comparison between PHT and PB.

In our systematic review, the results of this meta-analysis of RCTs showed no significant difference between PHT and other drugs when pairwise comparisons were carried out between PHT and VPA, LEV, or PB. In other words, it can be inferred that there is no difference in efficacy between PHT and other antiepileptic medications in terms of seizure cessation. One possible reason why the difference in the pairwise comparisons was not significant was a low statistical power due to the large number of studies with small case numbers in this study. For example, when comparing VPA and PHT, VPA was not significantly superior in seizure cessation, but it did show a greater tendency than PHT. A recently published RCT on SE has reported novel results: LEV, fosphenytoin, and VPA each led to seizure cessation and improved alertness at 60 min in approximately half of patients with benzodiazepine-refractory convulsive SE.[30]

In addition, our results showed significant heterogeneity in the comparison between PHT and PB. Among the results reported at this time, there were two RCTs comparing PHT

Table 2. Evidence profile comparing phenytoin with other drugs for status epilepticus

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PHT	Other medications	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation												
10	Randomized trials	Serious*	Not serious	Serious†	Not serious	None	313/485 (64.5%)	381/527 (72.3%)	RR 0.89 (0.82 to 0.97)	80 fewer per 1,000 (from 130 fewer to 22 fewer)	⊕⊕◯◯ Low	Critical
Mortality at discharge												
4	Randomized trials	Serious‡	Not serious	Serious†,§	Very serious¶	None	16/149 (10.7%)	15/149 (10.1%)	RR 1.07 (0.55 to 2.08)	7 more per 1,000 (from 45 fewer to 109 more)	⊕◯◯◯ Very low	Critical
Good neurological outcome												
2	Randomized trials	Serious**	Not serious	Serious††	Serious‡‡	None	30/52 (57.7%)	33/41 (80.5%)	RR 0.91 (0.72 to 1.15)	72 fewer per 1,000 (from 225 fewer to 121 more)	⊕◯◯◯ Very low	Critical

CI, confidence interval; RR, risk ratio.
*Allocation is not blinded in 2 cases, and concealment of allocation is not clear in 7 cases. The trial is being discontinued early in one case.
†The control antiepileptic drugs vary from study to study.
‡Allocation is not blinded in 1 case, and concealment of allocation is not clear in 3 cases.
§The outcome of one RCT was a 7-day mortality rate, with a large contribution rate of 47.5%.
¶Allocation is not blinded in one case, and concealment of allocation is not clear in one case.
**Different studies have different methods of assessing neurological outcomes.
††The sample size is smaller than OIS. Also, 95% CI contains considerable harm.
‡‡The sample size is smaller than OIS. Also, 95% CI includes both considerable benefits and harms.

and PB. Shaner et al. reported 36 consecutive patients with generalized convulsive SE who were treated with either a combination of diazepam (DZP) and PHT or PB.[27] The total time spent in active convulsive movements was shorter for the PB group than for the DZP/PHT group (median, 5 versus 9 min, $p < 0.06$). In all patients, however, convulsions were controlled within 7 h. Treiman et al. reported 570 patients with generalized convulsive SE who were randomly assigned to receive i.v. treatment with lorazepam, PB, PHT, or DZP followed by PHT. Among the 134 patients with a verified diagnosis of subtle generalized convulsive SE, no significant differences among the drugs were detected (range of success rates, 7.7–24.2%). In an intention-to-treat analysis, the differences among drugs were not significant, either among the patients with overt SE ($p = 0.12$) or among those with subtle SE ($p = 0.91$). Although the definition of seizures differed in these two RCTs, neither drug was significantly different in terms of its effects on seizure cessation. Therefore, the heterogeneity that existed between PHT and PB might have been due to the difference in the definition of seizures in these two reports.

Comparison with previous study

Two systematic reviews published in 2014[31] and 2019[32] compared the efficacy of five antiepileptic medications (VPA, lacosamide, LEV, PB, and PHT) as treatments for benzodiazepine-refractory convulsive SE. One study evaluated the efficacy and safety of i.v. VPA treatment for SE. Three randomized controlled trials compared i.v. VPA with i.v. PHT, two with i.v. diazepam, and one with i.v. PB. Valproate appeared to be an effective therapeutic option for patients with established benzodiazepine-refractory convulsive SE. However, no significant difference in seizure cessation was observed between PHT and VPA.[31] Additionally, another study aimed to estimate the comparative efficacy and safety of AEDs in adults with benzodiazepine-resistant convulsive SE. Five comparative RCTs were included, as follows: i.v. VPA versus PHT, i.v. LEV versus PHT, i.v. LCM versus VPA, DZP versus VPA, and PB versus VPA. The study results were reported according to the recommendations of the PRISMA extension statement for network meta-analyses. This study suggested that high-dose PB was effective at controlling SE and preventing seizure recurrence.[32] In that study, none of the included publications directly compared PB and PHT.

Our systematic review included more RCTs than either of the two prior reports. In addition, this study included a subgroup analysis of seizure cessation by pairwise comparison of PHT and VPA, LEV, or PB; no such analysis was reported in the previous studies.

Clinical implications

No significant difference was observed between PHT and VPA, LEV, or PB in terms of seizure cessation. Therefore, in clinical practice, clinicians may select the second-line treatment for adult SE from among these four drugs according to their customary practice and the insurance coverage available in the country.

Strengths and limitations

This study was the first systematic review to examine the effect of PHT on SE.

Nonetheless, the present study has several limitations. First, all but one of the included studies had small sample sizes.[28] Second, this study compares PHT to other AEDs but does not determine which AED is best. A network meta-analysis would be useful for addressing this question. Third, clinical rather than electroencephalographic criteria were used to determine the primary outcome of seizure cessation. Therefore, continuous electroencephalographic monitoring was not necessarily carried out. Finally, we were unable to assess the safety of the antiepileptic medications.

To date, no high-quality, evidence-based data are available to suggest the superiority of one AED over another in the treatment of benzodiazepine-refractory convulsive SE, and further head-to-head comparative studies are urgently needed.

CONCLUSIONS

The results of this meta-analysis of RCTs showed that i.v. PHT was significantly inferior to other medications in terms of the cessation of seizures. No significant differences were observed between PHT and other medications in terms of mortality or neurological outcomes in adult patients with SE.

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DISCLOSURE

Approval of the research protocol: N/A.
Informed consent: N/A.
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Animal studies: N/A.
Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. (A) Funnel plot of seizure cessation. (B) Funnel plot of mortality. (C) Funnel plot of a good neurological outcome.

File S1. Search strategies.