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Efficacy of anti-epileptic drugs in neonatal seizures: A systematic review protocol

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ABSTRACT

Introduction Seizures are one of the most common neurological disorders of neonates, which is also an emergency in the neonatal intensive care unit (NICU). For neonates, the recommended first-line anti-epileptic drugs (AEDs), includes phenobarbitone, which may be effective in only 50% of seizures. Some new AEDs, such as levetiracetam and valproic acid, have been studied in adults and older children. However, their efficacy for neonatal seizures remains uncertain. The aim of this investigation is to conduct a systematic review to evaluate the efficacy of all AEDs in neonates.

Method We will perform a systematic review including randomized controlled studies (RCTs), cohort studies, case-controlled studies, and case series studies which compared different AEDs, and single armed studies which evaluated the efficacy of AEDs in neonatal seizures. PubMed, Embase, Web of science, Cochrane Library and Clinical trial.gov will be searched. There will be no language restriction. Risk bias in RCTs will be evaluated by the Cochrane risk of bias tool, while cohort and case-control studies will be evaluated by the Newcastle-Ottawa Scale. A Network Meta-analysis will be performed by Bayesian model using WinBUGS V1.4.3 and R software if there is a high degree of homogeneity among studies. Otherwise, we will perform a narrative review without pooling.

Outcome The primary outcome will be seizure cessation. Secondary outcomes will be neonatal mortality during hospitalization and long-term neurodevelopmental outcome.

Ethics and dissemination Formal ethical approval is not required as no primary data are collected. This systematic review will be disseminated through a peer-reviewed publication.

Key words neonatal seizure; anti-seizure drugs; systematic review

What is already known on this topic?

- Phenobarbitone is the first-line therapy for neonatal seizures with uncertain efficacy and possible side effects
- New AEDs, such as levetiracetam, appear efficacy in neonatal seizures.

What this study hopes to add?

- The effectiveness of new AEDs compared to old one.
- The most common drug toxicity with different AEDs in neonates.

INTRODUCTION

Neonatal seizures are one of most common neurological complications in the neonatal intensive care unit (NICU), which have an incidence of 1-5 per 1000 live births in high income countries [1]. Epidemiological surveys for neonatal seizures in low income countries are scarce. A survey from Kenya indicated that the incidence rate was 39.5/1000 live births [2], which as anticipated is higher than in high income countries.

Neonatal seizures may be the manifestation of major neonatal diseases, such as hypoxic-ischemic encephalopathy (HIE), central nervous system infections or transient electrolyte disorders such as hypocalcaemia [3]. Continuous seizures can result in damage to the developing brain and may cause permanent neurological sequelae including cerebral palsy, epilepsy, mental retardation and cognitive delay [4,5]. These sequelae have a significant economic impact on both the family and society, for example, cerebral palsy costs $22,383 per year in the United States [6].

Although seizures in the newborn are considered as an emergency, the treatment of neonatal seizures is challenging. Phenobarbitone was used initially in neonates in 1912. A major advantage of phenobarbitone is its low cost and wide availability, which is of major importance in low and lower middle income countries. For example, a manual for Medical and Clinical Officers in Africa on seizures indicates phenobarbitone as the primary prescription, and also showed phenobarbitone remained the drug of choice in resource-poor settings [7]. Until now, phenobarbitone remains the first-line therapy for neonatal seizures around the world with uncertain efficacy and possible side effects [8,9]. Large-scale studies have showed 75.7%-98% neonates with seizures were treated by phenobarbitone initially [9,11]. However, more recent research suggests that seizures are controlled in only 43-50% neonates with phenobarbitone [12]. As an agonist of gamma aminobutyric acid (GABA) receptor, phenobarbitone increases GABA-mediated inhibition [13]. This is closely associated with its short-term side effect of central nervous system depression.

Furthermore, some experiments in vitro and rodents have reported that phenobarbitone may cause neuronal apoptosis [14,15], which may be the cause for long-term cognitive, motor and language delay [16].

Phenytoin was usually administered as second-line to phenobarbitone, which was initially introduced in 1938 [17,18]. Phenytoin is however associated with significant toxicity and its efficacy has been questioned [19,20]. Since then, new AEDs are being used in the treatment of neonatal seizures, for example, levetiracetam appears to be an effective AED of neonatal seizures, with seizure response rates ranging from 63% to 77% [21,22]. However, the evidence for the use of these AEDs in neonates is minimal.

A systematic review of the AEDs used in the treatment of neonatal seizures was published in 2013 but only included articles published up to August 2011. This systematic review included 16 articles (2 RCTs and 14 observational studies). They recommended phenobarbitone as first-line treatment [23]. Since then, there are likely to have been studies published, especially in relation to some of the newer AEDs. There is therefore a need for an updated systematic review to determine the most effective treatment for neonatal seizures.

METHODS

We will perform a systemic review and if possible, data synthesis will be done and network meta-analysis will be performed. We will follow Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-analyses guidelines. Otherwise, we will perform a narrative review without pooling if high heterogeneity exists. We will follow the PRISMA-P Checklist [24].

Eligibility criteria

Trial design: Randomized controlled trials (RCTs), cohort studies, case-controlled studies, and case series studies which compare different AEDs, and single arm studies which evaluate the efficacy of AEDs before and after administration will be included.

Participants

Neonates aged between 0 day and 28 days will be included. Seizures will be defined by clinical observation or electroencephalographic-confirmed.

Intervention

Any AEDs including first, second or even third-line medications, regardless of dose, routine, duration, frequency.

Comparison

Other AEDs or placebo

Outcomes

1.Primary outcome:

Seizure cessation

2. Second outcomes:

(1) Neonatal mortality during hospitalization.

(2) Long-term neurodevelopmental outcome including cerebral palsy, cognitive, motor and language delay.

Exclusion criteria

Pyridoxine dependence, severe congenital malformation and metabolic disorders, including electrolyte disturbance, hypocalcaemia and hypoglycemia, are excluded. Studies that do not provide details of seizure cessation and details of the neonates will be excluded.

Language: No language restrictions.

Search methods

The following databases will be searched: Pubmed, Embase, Web of Science, Cochrane Library and Clinical trial.gov. We will also screen the previous systemic review and related references for potential references. The Search term will combine medical subject heading (MeSH) and free word. MeSH terms are as follow: “Infant, Newborn”, “Seizures”, “Valproic Acid”, “Paraldehyde”, “Phenobarbitone”, “Levetiracetam”, “Lorazepam”, “Carbamazepine”, “Phenytoin”, “Midazolam”, “Lidocaine”, “Fosphenytoin”, “Bumetanide”. Detail for search strategy are listed in appendix 1.

Study records

Articles will be stored in ENDNOTE X9 software. Two reviewers (YH and MZ) will be responsible for reviewing references. After excluding irrelevant articles by title and

abstract, the full-text will be screened. Both reviewers will use the same inclusion and exclusion criteria for selecting full-texts. If there are disagreements, the opinions of a third review member will be obtained.

Risk of bias of individual study

The risk of bias of each trial will be investigated by two investigators (YH and MZ) independently. The third investigator (TX) will advise if there is disagreement. RCTs will be evaluated by the Cochrane risk of bias tool, while observational studies and case series will be evaluated by the Newcastle-Ottawa Scale and A Modified Delphi Technique separately.[25-27] See Appendix 2.

Data extraction

Data extraction will be performed by two investigators (YH and MZ) individually. Microsoft Excel 2010 will be used to record the extraction data. (Appendix 2).

Data analysis and synthesis

Odds ratio (OR), relative ratio (RR) and 95% confidence interval (CI) will be calculated for analysis. Heterogeneity will be measured by χ^2 test and I^2 statistic. 0% of I^2 means without heterogeneity, 0-25%, 25-50%, 75-100% of I^2 means low, moderate, high heterogeneity.[28] Whether the data can be synthesized is dependent on the heterogeneity of the primary study data:

1. If the primary outcome data and study design show a low and moderate heterogeneity, data will be synthesized. Additional subgroup and sensitivity analysis will be performed to find out the source of heterogeneity. Network meta-analysis will be conducted by bayesian model, using WinBUGS V1.4.3 and R software. And the surface under the cumulative ranking curve (SUCRA) will be calculated.
2. If it shows high heterogeneity ($I^2 \geq 75\%$) among studies for outcomes, synthesis of these data are limited. An updated systematic review will be done.

Analysis of subgroups

Subgroup analysis will be performed on first, second or even third-line AEDs of neonatal seizures.

Setting and participants

Patients and public were not involved in the development of this protocol.

ETHICS AND DISSEMINATION

Ethical approval is not required in this review. We will publish the results in a peer-reviewed journal.

FOOTNOTE

Authors' Contributors: YH contributed to developing and drafted the protocol. MZ contributed to developing the protocol. IC contributed to supervised the development of the protocol and revise the protocol. TX, SQ and JT contributed to revise the protocol. All the authors have approved the current protocol version.

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Competing interests None declared.

P**atient consent for publication:** Not required.

Ethics approval: There is no need for an ethical assessment because we only search and evaluate the existing literature.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: All the data relevant to the study are included in the article or uploaded as supplementary information.

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Appendix I.

Search strategy
(for each electronic database to be searched)

#1	Search terms	No of records returned
1	"Infant, Newborn"[Mesh] OR Newborn Infant OR Newborn Infants OR Newborns OR Newborn OR Neonate OR Neonates	
2	"Seizures"[Mesh] OR Seizure OR Nonepileptic Seizure OR Generalized Absence Seizures OR Tonic-Clonic Seizure OR Generalized Tonic-Clonic Seizures OR Clonic Seizure OR Tonic Seizures OR Atonic Seizure OR Atonic Absence Seizures OR Myoclonic Seizure OR Epileptic Seizure OR Absence Seizure OR Petit Mal Convulsion OR Convulsion OR Convulsive Seizures OR Motor Seizure OR Jacksonian Seizure OR Focal Seizure OR Partial Seizure OR Generalized Seizure OR Non-Epileptic Convulsion OR Complex Partial Seizures OR Single Seizures	
3	"Valproic Acid"[Mesh] OR 2-Propylpentanoic Acid OR Depakine OR Valproate Calcium OR Calcium Valproate OR Sodium Valproate OR Valproate Sodium OR Valproate OR Magnesium Valproate OR Ergenyl OR Propylisopropylacetic Acid OR Vupral OR Semisodium Valproate OR Divalproex Sodium OR Dipropyl Acetate OR Depakote OR Convulsofin OR Depakene OR Divalproex OR Propylpentanoic Acid	
4	"Paraldehyde"[Mesh] OR paraldehyde	
5	"Diazepam"[Mesh]OR 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-oneOR Relanium OR Apaurin OR Stesolid OR Sibazon OR Seduxen OR Valium OR Faustan OR Diazemuls	
6	"Phenobarbital"[Mesh] OR Phenylbarbital OR Gardenal OR Luminal OR Monosodium Salt Phenobarbital OR Phenobarbital	

	Sodium OR Hysteps OR Phenobarbitone OR Phenemal OR Phenylethylbarbituric Acid	
7	"Levetiracetam"[Mesh] OR S-isomer Etiracetam OR UcbL060 OR Ucb-L060 OR Ucb L060 OR Ucb L059 OR Ucb-L059 OR UCB 6474 OR UCB-6474 OR UCB6474 OR R-isomer Etiracetam OR Keppra OR Etiracetam OR alpha-ethyl-2-oxo-1-PyrrolidineacetamideOR alpha ethyl 2 oxo 1 Pyrrolidineacetamide	
8	"Lorazepam"[Mesh] OR Ativan OR Temesta OR Somagerol OR Apo Lorazepam OR Apo-Lorazepam OR WY4036 OR WY 4036 OR WY-4036 OR Sinestron OR Sedicepan OR Nu Loraz OR Nu-Loraz OR Novo Lorazem OR Novo-Lorazem OR Lorazepam Ratiopharm OR Lorazepam-Ratiopharm OR Lorazepam Neuraxpharm OR Lorazepam-Neuraxpharm OR Lorazepam Medical OR Lorazep Von Ct OR Laubeel OR Idalprem OR fidal Wyeth OR Durazolam OR Duralozam OR Donix OR Tolid OR Témesta	
9	"Carbamazepine"[Mesh] OR Carbamazepine Acetate OR Carbamazepine Phosphate OR Amizepine OR Tegretol OR Neurotol OR Finlepsin OR Epitol OR Carbazepin OR Carbamazepine Sulfate 2:1OR Carbamazepine Anhydrous OR Carbamazepine L-Tartrate 4:1OR Carbamazepine Hydrochloride OR Carbamazepine Dihydrate	
10	"Phenytoin"[Mesh]OR 5,5-Diphenylhydantoin OR Dilantin OR Antisacer OR Hydantol OR Epanutin OR Epamin OR Sodium Diphenylhydantoinate OR Phenytoin Sodium OR Dihydan OR Difenin OR Diphenylhydantoin OR 5,5-diphenylimidazolidine-2,4-dione OR Fenitoin	
11	"Midazolam"[Mesh] OR Midazolam Maleate OR Ro 213981 OR Ro 21 3981 OR Ro 21-3981 OR Midazolam Hydrochloride OR Versed OR Dormicum	

12	"Lidocaine"[Mesh] OR 2-Diethylamino-N-2,6-Dimethylphenyl Acetamide OR Dalcaine OR Xylocitin OR Xylocaine OR Xylesthesin OR Octocaine OR Lidocaine Sulfate 1:1 OR Xyloneural OR Lidocaine Monoacetate OR Lidocaine Monohydrochloride OR Lidocaine Hydrochloride OR Lidocaine Hydrocarbonate OR Lidocaine Carbonate OR Lidocaine Carbonate 2:1 OR Lignocaine OR 2-2EtN-2MePhAcN	
13	"fosphenytoin" [Supplementary Concept] OR 3-hydroxymethylphenytoin phosphate ester OR Cerebyx OR HMPDP OR 3-hydroxymethylphenytoin disodium phosphate OR fosphenytoin sodium OR Prodilantin OR ACC-9653 OR ACC 9653	
14	"Bumetanide"[Mesh] OR Bumethanide OR Burinex OR Bumedyl OR Miccil OR Fordiuran OR Drenural OR PF1593 OR Bumex OR PF-1593 OR PF 1593	
15	#1 AND #2	
16	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	
17	#15 and #16	
18	limit #17 to humans	

Appendix II. Data Extraction Form for Review and meta-analysis

Study Details	
General information	
• Title	
• First author	
• Year of publication	
• Journal	
• Country	
• Foundation	
• Study duration	
PICOs information	
• Study design (RCT, case-control, cohort)	
• Participants	
Sample size	
Day-age	
Gestational age	
Birth weight	
Diagnosis criteria	
Inclusion criteria	
• Intervention	
Type of AED	
Dose (Loading dose/ maintenance dose)	
Delivery route	
Duration	
Frequency	
• Comparison	
• Main outcome	
Primary outcome	
Mortality	
Long-term neurodevelopmental outcome	
Second outcome	
Cessation of seizure	
Exclusion criteria	

Risk of bias assessment (For RCT)

Domain	Description	Risk of bias
Election	1) Random sequence generation	a) High risk: Selection bias (biased allocation to interventions) due to inadequate generation of a randomize b) Low risk: Random sequence generation method should produce comparable groups c) Unclear risk: Not described in adequate detail
	2) Allocation concealment	a) High risk: Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment. b) Low risk: Intervention allocations likely could not have been foreseen in advance of, or during, enrollment c) Unclear risk: Not described in adequate detail
Reporting	1) Selective reporting	a) High risk: Reporting bias due to selective outcome reporting b) Low risk: Selective outcome reporting bias not detected c) Unclear risk: Insufficient information to permit judgement (It is likely that the majority of studies will fall into this category.)
Blindness	1) participants and personnel	a) High risk: Performance bias due to knowledge of the allocated interventions by participants and personnel during the study b) Low risk: Blinding was likely effective. c) Not described in adequate detail
	2) outcome assessment	a) High risk: Detection bias due to knowledge of the allocated interventions by outcome assessors. b) Low risk: Blinding was likely effective. c) Unclear risk: Not described in adequate detail
Attrition bias	1) Incomplete outcome data	a) High risk: Attrition bias due to amount, nature or handling of incomplete outcome data. b) Low risk：Handling of incomplete outcome data was complete and unlikely to have produced bias c) Unclear risk：Insufficient reporting of attrition/exclusions to permit judgment of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided)
Other bias	1) Other sources of bias	a) High risk: Bias due to problems not covered elsewhere in the table. b) Low risk: No other bias detected c) Unclear risk: There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.

Domain	Item	Score
election	1) Representativeness of the exposed cohort	a) truly representative of the average ___ (describe) in the community ✸ b) somewhat representative of the average____ in the community c) selected group of users eg nurses, volunteers ✸ d) no description of the derivation of the cohort
	2) Representativeness of the non-exposed cohort	a) drawn from the same community as the exposed cohort ✸ b) drawn from a different source c) no description of the derivation of the non-exposed cohort
	3) Ascertainment of exposure	a) secure record (eg: surgical records) ✸ b) structured interview ✸ c) written self-report d) no description
	4) Demonstration the outcome of interest was not present at start of study	a) yes ✸ b) no
Comparability	1) Comparability of cohort on the bases of the design or analysis	a) study controls for ___ (select the most important factor) ✸ b) study controls for any additional factor ✸ (These criteria could be modified to indicate specific control for a second important factor.)
Outcome	1) Assessment of outcome	a) independent blind assessment ✸ b) record linkage ✸ c) self-report d) no description
	2) Was follow-up long enough for outcomes to occur	a) yes (select an adequate follow up period for outcome of interest) ✸ b) no
	3) Adequacy of follow up of cohort	a) complete follow up - all subjects accounted for ✸ b) subjects lost to follow up unlikely to introduce bias - small number lost - > ___ % (select an adequate %) follow up, or description provided of those lost)✸ c) follow up rate < ___% (select an adequate %) and no description of those lost d) no statement
Quality scores		

Risk of Bias assessment (For cohort studies**)**

Domain	Item	Score
election	1) Representativeness of the exposed cohort	a) truly representative of the average ___ (describe) in the community ✸ b) somewhat representative of the average____ in the community c) selected group of users eg nurses, volunteers ✸ d) no description of the derivation of the cohort
	2) Representativeness of the non-exposed cohort	a) drawn from the same community as the exposed cohort ✸ b) drawn from a different source c) no description of the derivation of the non-exposed cohort
	3) Ascertainment of exposure	a) secure record (eg surgical records) ✸ b) structured interview ✸ c) written self-report d) no description
	4) Demonstration the outcome of interest was not present at start of study	a) yes ✸ b) no
Comparability	1) Comparability of cohort on the bases of the design or analysis	a) study controls for ___ (select the most important factor) ✸ b) study controls for any additional factor ✸ (These criteria could be modified to indicate specific control for a second important factor.)
Outcome	1) Assessment of outcome	a) independent blind assessment ✸ b) record linkage ✸ c) self-report d) no description
	2) Was follow-up long enough for outcomes to occur	a) yes (select an adequate follow up period for outcome of interest) ✸ b) no
	3) Adequacy of follow up of cohort	a) complete follow up - all subjects accounted for ✸ b) subjects lost to follow up unlikely to introduce bias - small number lost - > ___ % (select an adequate %) follow up, or description provided of those lost)✸ c) follow up rate < ___% (select an adequate %) and no description of those lost d) no statement
Quality scores		

Risk of Bias assessment (For case control studies)

Domain	Item	Score
Selection	1) Is the case definition adequate	a) yes, with independent validation✸ b) yes, eg record linkage or based on self-reports c) no description
	2) Representativeness of the cases	a) consecutive or obviously representative series of cases✸ b) potential for selection biases or not stated
	3) Selection of Controls	a) community controls ✸ b) hospital controls c) no description
	4) Definition of Controls	a) no history of disease (endpoint) ✸ b) no description of source
Comparability	1) Comparability of cases and controls on the bases of the design or analysis	a) study controls for ____ (Select the most important factor.)✸ b) study controls for any additional factor ✸ (These criteria could be modified to indicate specific control for a second important factor.)
Exposure	1) Ascertainment of exposure	a) secure record (eg surgical records) ✸ b) structured interview where blind to case/control status ✸ c) interview not blinded to case/control status d) written self-report or medical record only e) no description
	2) Same method of ascertainment for cases and controls	a) yes ✸ b) no
	3) Non-Response rate	a) same rate for both groups ✸ b) non respondents described c) rate different and no designation
Quality scores		

Risk of Bias assessment (For case series studies)

Domain1: Study design
1.Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?
Domain 2: Study population
2.Are the characteristics of the participants included in the study described?
3.Were the cases collected in more than one center?
4.Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?
5.Were participants recruited consecutively?
6.Did participants enter the study at a similar point in the disease?
Domain 3: Intervention and co-intervention
7.Was the intervention clearly described in the study?
8.Were additional interventions (co-interventions) clearly reported in the study?
Domain 4: Outcome measure
9. Are the outcome measures clearly defined in the introduction or methods section?
10.Were relevant outcomes appropriately measured with objective and/or subjective methods?
11.Were outcomes measured before and after intervention?
Domain 5: Statistical analysis
12.Were the statistical tests used to assess the relevant outcomes appropriate?
Domain 6: Results and conclusions
13.Was the length of follow-up reported?
14.Was the loss to follow-up reported?
15.Does the study provide estimates of the random variability in the data analysis of relevant outcomes?
16. Are adverse events reported?
17.Are the conclusions of the study supported by results?
Domain 7: Competing interests and sources of support
18. Are both competing interests and sources of support for the study reported?

Other information

	Description as stated in report/paper
Key conclusions	
Study funding sources	
Conflicts of interest	
References to other relevant studies	
Correspondence required for further study information	

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Efficacy of anti-epileptic drugs in neonatal seizures: A systematic review protocol

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Efficacy of anti-epileptic drugs in neonatal seizures: A systematic review protocol

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ABSTRACT

Introduction Seizures are one of the most common neurological disorders of neonates, which is also an emergency in the neonatal intensive care unit (NICU). For neonates, the recommended first-line anti-epileptic drugs (AEDs), includes phenobarbitone, which may be effective in only 50% of seizures. Some new AEDs, such as levetiracetam, have been shown to be effective in adults and older children. However, their efficacy for neonatal seizures remains uncertain. The aim of this investigation is to conduct a systematic review to evaluate the efficacy of all AEDs in neonates. Additionally, the long term outcomes following neonatal seizures, in relation to the development of cerebral palsy and epilepsy will be studied.

Method We will perform a systematic review including randomized controlled studies (RCTs), cohort studies, case-controlled studies, and case series studies which evaluated the efficacy of AEDs and short term and long term outcomes in neonatal seizures. PubMed, Embase, Web of science, Cochrane Library and Clinical trial.gov will be searched. There will be no language restriction. Risk bias in RCTs will be evaluated by the Cochrane risk of bias tool, while cohort and case-control studies will be evaluated by the Newcastle-Ottawa Scale. A Network Meta-analysis will be performed by Bayesian model using WinBUGS V1.4.3 and R software if there is a high degree of homogeneity among studies. Otherwise, we will perform a narrative review without pooling. Subgroup analyses will be performed in different AEDs and dosage groups.

Outcome The primary outcomes will be seizure cessation confirmed by electroencephalogram and long-term neurodevelopmental outcome.. Secondary outcomes will be neonatal mortality during hospitalization and suspected drug toxicity.

Ethics and dissemination Formal ethical approval is not required as no primary data are collected. This systematic review will be disseminated through a peer-reviewed publication.

Key words neonatal seizure; anti-seizure drugs; systematic review

What is already known on this topic?

- Phenobarbitone is the first-line therapy for neonatal seizures with uncertain efficacy and possible side effects
- New AEDs, such as levetiracetam, appear efficacy in neonatal seizures.
- Neonatal seizures are associated with the development of cerebral palsy and epilepsy

What this study hopes to add?

- The effectiveness of new AEDs compared to old ones.
- Long term outcomes in relation to cerebral palsy and epilepsy following neonatal seizures
- The most common drug toxicity with different AEDs in neonates.

INTRODUCTION

Neonatal seizures are one of most common neurological complications in the neonatal intensive care unit (NICU), which have an incidence of 1-5 per 1000 live births in high income countries[1]. Epidemiological surveys for neonatal seizures in low income countries are scarce. A survey from Kenya indicated that the incidence rate was 39.5/1000 live births[2], which as anticipated is higher than in high income countries.

Neonatal seizures may be the manifestation of major neonatal diseases, such as hypoxic-ischemic encephalopathy (HIE), central nervous system infections, genetic disorders, hypoglycaemia or transient electrolyte disorders such as hypocalcaemia[3]. Continuous seizures can result in damage to the developing brain and may cause permanent neurological sequelae including cerebral palsy (CP), epilepsy, mental retardation and cognitive delay[4,5]. These sequelae have a significant economic impact on both the family and society, for example, CP costs $22,383 per year in the United States[6].

Although seizures in the newborn are considered as an emergency, the treatment of neonatal seizures is challenging. Phenobarbitone was used initially in neonates in 1912. A major advantage of phenobarbitone is its low cost and wide availability, which is of major importance in low and lower middle income countries. For example, a manual for Medical and Clinical Officers in Africa on seizures indicates phenobarbitone as the primary prescription, and also showed phenobarbitone remained the drug of choice in resource-poor settings[7]. Until now, phenobarbitone remains the first-line therapy for neonatal seizures around the world with uncertain efficacy and possible side effects[8,9]. Large-scale studies have showed 75.7%-98% neonates with seizures were treated by phenobarbitone initially[9-11]. However, more recent research suggests that seizures are controlled in only 43-50% neonates with phenobarbitone[12]. As an agonist of gamma aminobutyric acid (GABA) receptor, phenobarbitone increases GABA-mediated inhibition[13]. This is closely associated with its short-term side effect of central nervous system depression. Furthermore, some experiments in vitro and rodents have reported that phenobarbitone may cause neuronal apoptosis [14,15], which

may be the cause for long-term cognitive, motor and language delay[16].

Phenytoin was usually administered as second-line to phenobarbitone, which was initially introduced in 1938[17,18]. Phenytoin is however associated with significant toxicity and its efficacy has been questioned[19,20]. Since then, new AEDs are being used in the treatment of neonatal seizures, for example, levetiracetam appears to be an effective AED of neonatal seizures, with seizure response rates ranging from 63% to 77%[21,22]. However, the evidence for the use of these AEDs in neonates is minimal.

A systematic review of the AEDs used in the treatment of neonatal seizures was published in 2013 but only included articles published up to August 2011. This systematic review included 16 articles (2 RCTs and 14 observational studies). They recommended phenobarbitone as first-line treatment [23]. Since then, there are likely to have been studies published, especially in relation to some of the newer AEDs. There is therefore a need for an updated systematic review to determine the most effective treatment for neonatal seizures.

Additionally, the long term outcomes of CP and epilepsy following neonatal seizures is not clear. A large single centre prospective cohort study of 82 neonates with acute seizures was published in 2007[5]. There is a need for a systematic review on the long term outcomes following neonatal seizures.

METHODS

We will perform a systemic review and if possible, data synthesis will be done and network meta-analysis will be performed. We will follow Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-analyses guidelines. Otherwise, we will perform a narrative review without pooling if high heterogeneity exists. We will follow the PRISMA-P Checklist[24].

Eligibility criteria

Trial design: Any original study (i.e. cohort, case-control, cross-sectional), descriptive designs (i.e. case series and case report) that provides information about AEDs for neonatal seizure and the short-term and long-term outcomes.

Participants

Neonates aged between 0 day and 28 days will be included. Seizures will be defined by confirmed electroencephalographic (EEG).

Intervention

Any AEDs including first, second or even third-line medications, regardless of dose, routine, duration, frequency. Subgroup analysis of the effect of dose will be performed on both short term and long term outcomes, if feasible.

Comparison

Other AEDs or placebo

Outcomes

1.Primary outcome:

(1) Short term Seizure cessation – confirmed by EEG

(2) Long-term neurodevelopmental outcome including CP, learning disability and epilepsy.

2. Second outcomes:

(1) Neonatal mortality during hospitalization.

(2) Drug toxicity

Exclusion criteria

Pyridoxine dependence, severe congenital malformation and metabolic disorders, including electrolyte disturbance, hypocalcaemia and hypoglycemia, are excluded. Studies that do not provide details of seizure cessation and details of the neonates will be excluded.

Language: No language restrictions.

Search methods

The following databases will be searched: Pubmed, Embase, Web of Science, Cochrane Library and Clinical trial.gov. We will also screen the previous systemic review and related references for potential references. The Search term will combine medical subject heading (MeSH) and free word. MeSH terms are as follow: “Infant, Newborn”, “Seizures”, “Valproic Acid”, “Paraldehyde”, “Phenobarbitone”, “Levetiracetam”,

"Lorazepam", "Carbamazepine", "Phenytoin", "Midazolam", "Lidocaine", "Fosphenytoin", "Bumetanide". Detail for search strategy are listed in Appendix 1.

Study records

Articles will be stored in ENDNOTE X9 software. Two reviewers (YH and MZ) will be responsible for reviewing references. After excluding irrelevant articles by title and abstract, the full-text will be screened. Both reviewers will use the same inclusion and exclusion criteria for selecting full-texts. If there are disagreements, the opinions of a third review member will be obtained.

Risk of bias of individual study

The risk of bias of each trial will be investigated by two investigators (YH and MZ) independently. The third investigator (TX) will advise if there is disagreement. RCTs will be evaluated by the Cochrane risk of bias tool, while observational studies and case series will be evaluated by the Newcastle-Ottawa Scale and A Modified Delphi Technique separately[25-27]. See Appendix 2.

Data extraction

Data extraction will be performed by two investigators (YH and MZ) individually. Microsoft Excel 2010 will be used to record the extraction data.

The following data will be extracted:

1. General information: author, year(s) the study took place, year of publication, country, sample size, participants' basic information.
2. Study methodology: study design, included/excluded criteria for participants.
3. Details of AEDs medication of neonatal seizures: Type of AED; Dosage; Delivery route; Duration; Frequency.
4. Outcomes relevant to this review: The cessation rates; toxicity; mortality rates; long-term neurodevelopmental outcome, including the population who developed CP, learning difficulties and epilepsy.

Data analysis and synthesis

Odds ratio (OR), relative ratio (RR) and 95% confidence interval (CI) will be

calculated for analysis. Seizure cessation, CP and epilepsy following neonatal seizure will be used combined. Heterogeneity will be measured by χ^2 test and I^2 statistic. 0% of I^2 means without heterogeneity, 0-25%, 25-50%, 75-100% of I^2 means low, moderate, high heterogeneity[28]. Whether the data can be synthesized is dependent on the heterogeneity of the primary study data:

1. If the primary outcome data and study design show a low and moderate heterogeneity, data will be synthesized. Additional subgroup and sensitivity analysis will be performed to find out the source of heterogeneity. Network meta-analysis will be conducted by bayesian model, using WinBUGS V1.4.3 and R software. And the surface under the cumulative ranking curve (SUCRA) will be calculated.
2. If it shows high heterogeneity (I^2≥75%) among studies for outcomes, synthesis of these data are limited. An updated systematic review will be done.

Analysis of subgroups

Subgroup analysis will be performed on first, second or even third-line AEDs of neonatal seizures. Subgroup analysis will also be performed on the dosage of individual AEDs.

Setting and participants

Patients and public were not involved in the development of this protocol.

ETHICS AND DISSEMINATION

Ethical approval is not required in this review. We will publish the results in a peer-reviewed journal.

DISCUSSION

The systematic review should hopefully provide evidence about the optimal management of neonatal seizures. Where there is uncertainty, this information should be of benefit in prioritising future areas of research.

The development of long term outcomes will be of benefit in determining the importance of the management of acute seizures in the neonatal period. This will be of

benefit to both health professionals and parents.

FOOTNOTE

Authors' Contributors: YH contributed to developing and drafted the protocol. MZ contributed to developing the protocol. IC contributed to supervised the development of the protocol and revise the protocol. TX, SQ and JT contributed to revise the protocol. All the authors have approved the current protocol version.

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Competing interests None declared.

P**atient consent for publication:** Not required.

Ethics approval: There is no need for an ethical assessment because we only search and evaluate the existing literature.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: All the data relevant to the study are included in the article or uploaded as supplementary information.

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Appendix I.

Search strategy
(for each electronic database to be searched)

#1	Search terms	No of records returned
1	"Infant, Newborn"[Mesh] OR Newborn Infant OR Newborn Infants OR Newborns OR Newborn OR Neonate OR Neonates	
2	"Seizures"[Mesh] OR Seizure OR Nonepileptic Seizure OR Generalized Absence Seizures OR Tonic-Clonic Seizure OR Generalized Tonic-Clonic Seizures OR Clonic Seizure OR Tonic Seizures OR Atonic Seizure OR Atonic Absence Seizures OR Myoclonic Seizure OR Epileptic Seizure OR Absence Seizure OR Petit Mal Convulsion OR Convulsion OR Convulsive Seizures OR Motor Seizure OR Jacksonian Seizure OR Focal Seizure OR Partial Seizure OR Generalized Seizure OR Non-Epileptic Convulsion OR Complex Partial Seizures OR Single Seizures	
3	"Valproic Acid"[Mesh] OR 2-Propylpentanoic Acid OR Depakine OR Valproate Calcium OR Calcium Valproate OR Sodium Valproate OR Valproate Sodium OR Valproate OR Magnesium Valproate OR Ergenyl OR Propylisopropylacetic Acid OR Vupral OR Semisodium Valproate OR Divalproex Sodium OR Dipropyl Acetate OR Depakote OR Convulsofin OR Depakene OR Divalproex OR Propylpentanoic Acid	
4	"Paraldehyde"[Mesh] OR paraldehyde	
5	"Diazepam"[Mesh]OR 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-oneOR Relanium OR Apaurin OR Stesolid OR Sibazon OR Seduxen OR Valium OR Faustan OR Diazemuls	
6	"Phenobarbital"[Mesh] OR Phenylbarbital OR Gardenal OR Luminal OR Monosodium Salt Phenobarbital OR Phenobarbital	

	Sodium OR Hysteps OR Phenobarbitone OR Phenemal OR Phenylethylbarbituric Acid	
7	"Levetiracetam"[Mesh] OR S-isomer Etiracetam OR UcbL060 OR Ucb-L060 OR Ucb L060 OR Ucb L059 OR Ucb-L059 OR UCB 6474 OR UCB-6474 OR UCB6474 OR R-isomer Etiracetam OR Keppra OR Etiracetam OR alpha-ethyl-2-oxo-1-PyrrolidineacetamideOR alpha ethyl 2 oxo 1 Pyrrolidineacetamide	
8	"Lorazepam"[Mesh] OR Ativan OR Temesta OR Somagerol OR Apo Lorazepam OR Apo-Lorazepam OR WY4036 OR WY 4036 OR WY-4036 OR Sinestron OR Sedicepan OR Nu Loraz OR Nu-Loraz OR Novo Lorazem OR Novo-Lorazem OR Lorazepam Ratiopharm OR Lorazepam-Ratiopharm OR Lorazepam Neuraxpharm OR Lorazepam-Neuraxpharm OR Lorazepam Medical OR Lorazep Von Ct OR Laubeel OR Idalprem OR fidal Wyeth OR Durazolam OR Duralozam OR Donix OR Tolid OR Témesta	
9	"Carbamazepine"[Mesh] OR Carbamazepine Acetate OR Carbamazepine Phosphate OR Amizepine OR Tegretol OR Neurotol OR Finlepsin OR Epitol OR Carbazepin OR Carbamazepine Sulfate 2:1OR Carbamazepine Anhydrous OR Carbamazepine L-Tartrate 4:1OR Carbamazepine Hydrochloride OR Carbamazepine Dihydrate	
10	"Phenytoin"[Mesh]OR 5,5-Diphenylhydantoin OR Dilantin OR Antisacer OR Hydantol OR Epanutin OR Epamin OR Sodium Diphenylhydantoinate OR Phenytoin Sodium OR Dihydan OR Difenin OR Diphenylhydantoin OR 5,5-diphenylimidazolidine-2,4-dione OR Fenitoin	
11	"Midazolam"[Mesh] OR Midazolam Maleate OR Ro 213981 OR Ro 21 3981 OR Ro 21-3981 OR Midazolam Hydrochloride OR Versed OR Dormicum	

12	"Lidocaine"[Mesh] OR 2-Diethylamino-N-2,6-Dimethylphenyl Acetamide OR Dalcaine OR Xylocitin OR Xylocaine OR Xylesthesin OR Octocaine OR Lidocaine Sulfate 1:1 OR Xyloneural OR Lidocaine Monoacetate OR Lidocaine Monohydrochloride OR Lidocaine Hydrochloride OR Lidocaine Hydrocarbonate OR Lidocaine Carbonate OR Lidocaine Carbonate 2:1 OR Lignocaine OR 2-2EtN-2MePhAcN	
13	"fosphenytoin" [Supplementary Concept] OR 3-hydroxymethylphenytoin phosphate ester OR Cerebyx OR HMPDP OR 3-hydroxymethylphenytoin disodium phosphate OR fosphenytoin sodium OR Prodilantin OR ACC-9653 OR ACC 9653	
14	"Bumetanide"[Mesh] OR Bumethanide OR Burinex OR Bumedyl OR Miccil OR Fordiuran OR Drenural OR PF1593 OR Bumex OR PF-1593 OR PF 1593	
15	#1 AND #2	
16	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	
17	#15 and #16	
18	limit #17 to humans	

Appendix II. Data Extraction Form for Review and meta-analysis

Study Details	
General information	
• Title	
• First author	
• Year of publication	
• Journal	
• Country	
• Foundation	
• Study duration	
PICOs information	
• Study design (RCT, case-control, cohort)	
• Participants	
Sample size	
Day-age	
Gestational age	
Birth weight	
Diagnosis criteria	
Inclusion criteria	
• Intervention	
Type of AED	
Dose (Loading dose/ maintenance dose)	
Delivery route	
Duration	
Frequency	
• Comparison	
• Main outcome	
Primary outcome	
Mortality	
Long-term neurodevelopmental outcome	
Second outcome	
Cessation of seizure	
Exclusion criteria	

Risk of bias assessment (For RCT)

Domain	Description	Risk of bias
Election	1) Random sequence generation	a) High risk: Selection bias (biased allocation to interventions) due to inadequate generation of a randomize b) Low risk: Random sequence generation method should produce comparable groups c) Unclear risk: Not described in adequate detail
	2) Allocation concealment	a) High risk: Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment. b) Low risk: Intervention allocations likely could not have been foreseen in advance of, or during, enrollment c) Unclear risk: Not described in adequate detail
Reporting	1) Selective reporting	a) High risk: Reporting bias due to selective outcome reporting b) Low risk: Selective outcome reporting bias not detected c) Unclear risk: Insufficient information to permit judgement (It is likely that the majority of studies will fall into this category.)
Blindness	1) participants and personnel	a) High risk: Performance bias due to knowledge of the allocated interventions by participants and personnel during the study b) Low risk: Blinding was likely effective. c) Not described in adequate detail
	2) outcome assessment	a) High risk: Detection bias due to knowledge of the allocated interventions by outcome assessors. b) Low risk: Blinding was likely effective. c) Unclear risk: Not described in adequate detail
Attrition bias	1) Incomplete outcome data	a) High risk: Attrition bias due to amount, nature or handling of incomplete outcome data. b) Low risk：Handling of incomplete outcome data was complete and unlikely to have produced bias c) Unclear risk：Insufficient reporting of attrition/exclusions to permit judgment of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided)
Other bias	1) Other sources of bias	a) High risk: Bias due to problems not covered elsewhere in the table. b) Low risk: No other bias detected c) Unclear risk: There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.

Domain	Item	Score
election	1) Representativeness of the exposed cohort	a) truly representative of the average ___ (describe) in the community ✸ b) somewhat representative of the average____ in the community c) selected group of users eg nurses, volunteers ✸ d) no description of the derivation of the cohort
	2) Representativeness of the non-exposed cohort	a) drawn from the same community as the exposed cohort ✸ b) drawn from a different source c) no description of the derivation of the non-exposed cohort
	3) Ascertainment of exposure	a) secure record (eg: surgical records) ✸ b) structured interview ✸ c) written self-report d) no description
	4) Demonstration the outcome of interest was not present at start of study	a) yes ✸ b) no
Comparability	1) Comparability of cohort on the bases of the design or analysis	a) study controls for ___ (select the most important factor) ✸ b) study controls for any additional factor ✸ (These criteria could be modified to indicate specific control for a second important factor.)
Outcome	1) Assessment of outcome	a) independent blind assessment ✸ b) record linkage ✸ c) self-report d) no description
	2) Was follow-up long enough for outcomes to occur	a) yes (select an adequate follow up period for outcome of interest) ✸ b) no
	3) Adequacy of follow up of cohort	a) complete follow up - all subjects accounted for ✸ b) subjects lost to follow up unlikely to introduce bias - small number lost - > ___ % (select an adequate %) follow up, or description provided of those lost)✸ c) follow up rate < ___% (select an adequate %) and no description of those lost d) no statement
Quality scores		

Risk of Bias assessment (For cohort studies**)**

Domain	Item	Score
election	1) Representativeness of the exposed cohort	a) truly representative of the average ___ (describe) in the community ✸ b) somewhat representative of the average____ in the community c) selected group of users eg nurses, volunteers ✸ d) no description of the derivation of the cohort
	2) Representativeness of the non-exposed cohort	a) drawn from the same community as the exposed cohort ✸ b) drawn from a different source c) no description of the derivation of the non-exposed cohort
	3) Ascertainment of exposure	a) secure record (eg surgical records) ✸ b) structured interview ✸ c) written self-report d) no description
	4) Demonstration the outcome of interest was not present at start of study	a) yes ✸ b) no
Comparability	1) Comparability of cohort on the bases of the design or analysis	a) study controls for ___ (select the most important factor) ✸ b) study controls for any additional factor ✸ (These criteria could be modified to indicate specific control for a second important factor.)
Outcome	1) Assessment of outcome	a) independent blind assessment ✸ b) record linkage ✸ c) self-report d) no description
	2) Was follow-up long enough for outcomes to occur	a) yes (select an adequate follow up period for outcome of interest) ✸ b) no
	3) Adequacy of follow up of cohort	a) complete follow up - all subjects accounted for ✸ b) subjects lost to follow up unlikely to introduce bias - small number lost - > ___ % (select an adequate %) follow up, or description provided of those lost) ✸ c) follow up rate < ___% (select an adequate %) and no description of those lost d) no statement
Quality scores		

Risk of Bias assessment (For case control studies)

Domain	Item	Score
Selection	1) Is the case definition adequate	a) yes, with independent validation✸ b) yes, eg record linkage or based on self-reports c) no description
	2) Representativeness of the cases	a) consecutive or obviously representative series of cases✸ b) potential for selection biases or not stated
	3) Selection of Controls	a) community controls ✸ b) hospital controls c) no description
	4) Definition of Controls	a) no history of disease (endpoint) ✸ b) no description of source
Comparability	1) Comparability of cases and controls on the bases of the design or analysis	a) study controls for ____ (Select the most important factor.)✸ b) study controls for any additional factor ✸ (These criteria could be modified to indicate specific control for a second important factor.)
Exposure	1) Ascertainment of exposure	a) secure record (eg surgical records) ✸ b) structured interview where blind to case/control status ✸ c) interview not blinded to case/control status d) written self-report or medical record only e) no description
	2) Same method of ascertainment for cases and controls	a) yes ✸ b) no
	3) Non-Response rate	a) same rate for both groups ✸ b) non respondents described c) rate different and no designation
Quality scores		

Risk of Bias assessment (For case series studies)

Domain1: Study design
1.Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?
Domain 2: Study population
2.Are the characteristics of the participants included in the study described?
3.Were the cases collected in more than one center?
4.Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?
5.Were participants recruited consecutively?
6.Did participants enter the study at a similar point in the disease?
Domain 3: Intervention and co-intervention
7.Was the intervention clearly described in the study?
8.Were additional interventions (co-interventions) clearly reported in the study?
Domain 4: Outcome measure
9. Are the outcome measures clearly defined in the introduction or methods section?
10.Were relevant outcomes appropriately measured with objective and/or subjective methods?
11.Were outcomes measured before and after intervention?
Domain 5: Statistical analysis
12.Were the statistical tests used to assess the relevant outcomes appropriate?
Domain 6: Results and conclusions
13.Was the length of follow-up reported?
14.Was the loss to follow-up reported?
15.Does the study provide estimates of the random variability in the data analysis of relevant outcomes?
16. Are adverse events reported?
17.Are the conclusions of the study supported by results?
Domain 7: Competing interests and sources of support
18. Are both competing interests and sources of support for the study reported?

Other information

	Description as stated in report/paper
Key conclusions	
Study funding sources	
Conflicts of interest	
References to other relevant studies	
Correspondence required for further study information	