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Efficacy of antiepileptic 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. For neonates, the recommended first-line antiepileptic drugs (AEDs) include 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 randomised 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 the Bayesian model using WinBUGS V.1.4.3 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 hospitalisation 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.

What is already known on this topic?

- Phenobarbitone is the first-line therapy for neonatal seizures with uncertain efficacy and possible side effects.
- New antiepileptic drugs (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 with 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–ischaemic encephalopathy, 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 US$22 383 per year in the USA.[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 shown that 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 are 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 and Meta-Analyses (PRISMA) 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 (ie, cohort, case control, cross sectional), descriptive designs (ie, 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-line, second-line or even third-line medications, regardless of dose, routine, duration and 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

Primary outcome

1. Short term seizure cessation—confirmed by EEG.
2. Long-term neurodevelopmental outcome including CP, learning disability and epilepsy.

Second outcomes

1. Neonatal mortality during hospitalisation.
2. Drug toxicity.

Exclusion criteria

Pyridoxine dependence, severe congenital malformation and metabolic disorders, including electrolyte disturbance, hypocalcaemia and hypoglycaemic, 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 follows: “Infant, Newborn”, “Seizures”, “Valproic Acid”, “Paraldehyde”, “Phenobarbitone”, “Levetiracetam”, “Lorazepam”, “Carbamazepine”, “Phenytoin”, “Midazolam”, “Lidocaine”, “Fosphenytoin”, “Bumetanide”. Detail for search strategy is listed in online supplementary appendix 1.

Study records

Articles will be stored in EndNote V.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 online supplementary 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

OR, relative ratio and 95% 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. Zero per cent of I^2 means without heterogeneity; 0%–25%, 25%–50% and 75%–100% of I^2 means low, moderate and high heterogeneity, respectively.[28] Whether the data can be synthesised 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 synthesised. Additional subgroup and sensitivity analysis will be performed to find out the source of heterogeneity. Network meta-analysis will be conducted by the Bayesian model, using WinBUGS V.1.4.3 and R software. And the surface under the cumulative ranking curve will be calculated.
2. If it shows high heterogeneity ($I^2 \geq 75\%$) among studies for outcomes, synthesis of these data is limited. An updated systematic review will be done.

Analysis of subgroups

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

Patient and public involvement

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

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.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement No data are available. All the data relevant to the study are included in the article or uploaded as supplementary information.

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