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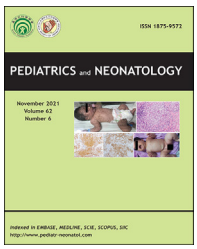

Original Article

Comparative efficacy of anti-epileptic drugs for neonatal seizures: A network meta-analysis

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Key Words
Anti-epileptic drugs;
Levetiracetam;
Neonatal seizures;
Phenobarbital

Background: Anti-epileptic drugs have different effects on neonatal seizures, and new agents have been widely used in recent years. Meanwhile, significant differences still exist in the treatment for neonatal seizures, whether in choice of drug or in duration of treatment. And with the increase in options for treatment, the best choice of second-line treatment has not been recommended.
Methods: The MEDLINE, the Cochrane Library, Web of Science, Embase and clinicaltrials.gov databases were searched (January 1, 1960 to October 20, 2020). Randomized controlled trials (RCTs) or observational investigations studying anti-epileptic drugs for neonatal seizures were selected. And then we conducted a network meta-analysis and examined comparative efficacy of the first-line and second-line anti-epileptic drugs for neonatal seizures.
Results: Data were extracted from 11 included studies by 2 independent investigators. Random effects models were used to estimate odds ratios (ORs). We performed direct meta-analyses with a random effects model and network meta-analyses for first-line and second-line drugs. Five published RCTs and 6 observational investigations with 1333 patients and 6 interventions contributed to the analysis.

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Conclusion: We recommend phenobarbital as the first-line drug for neonatal seizures. In addition, there is a tendency for levetiracetam to be an effective second-line treatment for neonatal seizures after failure of first-line drugs.

1. Introduction

Seizures, a neurological emergency, affect approximately 1.5–5 per 1000 live births in term newborns[1–3] and 57.5 to 132 per 1000 live births in premature infants.[4] It is a symptom of neurological dysfunction,[5] and infants in the neonatal period are at particularly high risk of seizures compared with other age groups.[4] Increasing evidence supports the notion that a higher risk of long-term neurodevelopmental disabilities may occur when seizures are present in newborns.[6,7]

The most widely used anti-epileptic drug is phenobarbital, which is often applied as a first-line treatment. However, the clinical control for neonatal seizures with the use of the two widely used anti-epileptic drugs (phenobarbital and phenytoin) is only achieved in 50–70% of newborns,[8] with even less control in most neonatal electrical seizures. In addition, there are also concerns about short-term side effects, potentially abnormal neurodevelopment, and medication interactions.[9,10] New agents, such as levetiracetam and topiramate, have been gradually and widely used in recent years, although their pharmacokinetic data, efficacy, and short- or long-term side effects are limited.[11] However, significant differences still exist in the treatment for neonatal seizures, whether in choice of drug or in duration of treatment.[12–14]

Although the common strategy of optimal pharmacological treatment for neonatal seizures has been published in recent years, more reliable data are still needed to support it.[15,16] With the increase in options for treatment, the best choice of second-line treatment has not been recommended. Therefore, we performed a network meta-analysis to comprehensively compare and rank first-line and second-line anti-epileptic drugs for the treatment of seizures in neonates.

2. Methods

2.1. Search strategy

We searched for relevant randomized trials and observational investigations in the Cochrane Central Register of Controlled Trials (Cochrane Library 2020, issue 7), including Epilepsy Group's specialized register, Web of Science (1960 to October 2020), MEDLINE (via PubMed) (1960 to October 2020), EMBASE (1960 to October 2020), and clinicaltrials.gov. The search terms included infant or newborn or neonat*, seizure* or epilepsy* or convulsion*, anticonvulsant* or antiepileptic*. The search terms and limits are provided in the Supporting Information (Table e–1- Table e–5).

2.2. Study selection

We included published and unpublished controlled trials utilizing either random or quasi-random patient allocation and observational investigations examining phenobarbital, benzodiazepines (midazolam, clonazepam, diazepam, lorazepam), phenytoin, levetiracetam, lidocaine, carbamazepine, and lamotrigine, which recruited neonates with clinical and/or electrographic seizures commencing within the first 28 days of life.

We excluded studies with a focus on seizures due to electrolyte disturbances (e.g., hypoglycemia, correctable hypocalcemia), metabolic disorders (e.g., nonketotic hyperglycinemia, pyridoxine deficiency), or opioid withdrawal because these seizures secondary to these diseases responded to correction of hypoglycemia, hypocalcemia, or any other metabolic disorder well. Review articles without primary data, case reports, and nonpeer reviewed articles consisting of meeting abstracts were excluded. Whenever a study included other age groups without specific outcomes of newborns or failed to include seizure cessation as an outcome, it was also excluded. Additional exclusion criteria included studies with an overall sample size of fewer than 10 patients.

2.3. Standard protocol approvals, registrations

This study is registered with PROSPERO, number CRD42018116311.

2.4. Quality assessment and data collection

To identify relevant studies, two reviewers independently screened the results of the searches and applied inclusion criteria using a structured form. Then, they independently extracted data from relevant studies using a predetermined data extraction form and cross-checked to reach a consensus. The following variables were recorded: (i) characteristics of participants (including gestational age), (ii) type of intervention (including dose), and (iii) type of outcome measure. If necessary, the primary authors were contacted to retrieve additional information. Discrepancies were resolved through discussion or in consultation with a third reviewer. They independently assessed the quality of the included studies using the Cochrane risk-of-bias tool for randomized clinical trials[18] and the Newcastle Ottawa Scale (NOS) for observational studies.[19] According to the NOS, the

study quality was assessed as low (0—3 points), medium (4—6 points), or high (7—9 points).

2.5. Outcome measures

The primary efficacy endpoint, specified a priori, was the control of clinical or electrographic seizures in 72 h. Secondary outcomes included mortality rate and long-term adverse effects consisting of cerebral palsy, mental retardation, etc.

2.6. Statistical analysis

First, direct meta-analysis for anti-epileptic treatment comparisons was performed with STATA. Dichotomous outcomes were calculated by the odds ratio (OR) with 95% CI, and continuous outcomes were calculated by the standardized mean difference (SMD) if necessary. Statistical heterogeneity of each direct meta-analysis was assessed with the I^2 statistic and p value.[20] In addition, publication bias was detected by STATA using a funnel plot and Egger's test. Second, we performed a network meta-analysis using a random-effects model with STATA, and the results of the network meta-analysis were reported by effect sizes (ORs) with 95% CIs. We assessed the differences between direct and indirect evidence by calculating the difference between direct and indirect comparisons in closed loops.[21] Meanwhile, the node splitting method, which compared direct and indirect evidence in each combination of drugs, was also used to evaluate the inconsistency.[22,23] Moreover, the surface under the cumulative ranking curve (SUCRA) was detected to evaluate the rank probability for each anti-epileptic treatment on different outcomes.[24] To detect whether there was dominant publication bias in the network meta-analysis, we made a comparison-adjusted funnel plot for various outcomes.

2.7. Data availability statement

Any data not published within the article are available in a public repository and include digital object identifiers (doi) or accession numbers to the datasets or to state that anonymized data will be shared by request from any qualified investigator.

3. Result

3.1. Search results

Overall, 10267 citations were confirmed by the search, and 305 potentially eligible articles were requested in the full text (Table 1). A total of 296 reports, including 3 ongoing clinical trials for which we could not obtain the relevant data, were excluded, resulting in 11 studies (1331 patients) describing 7 anti-epileptic drugs.[25—34]

3.2. Study characteristics

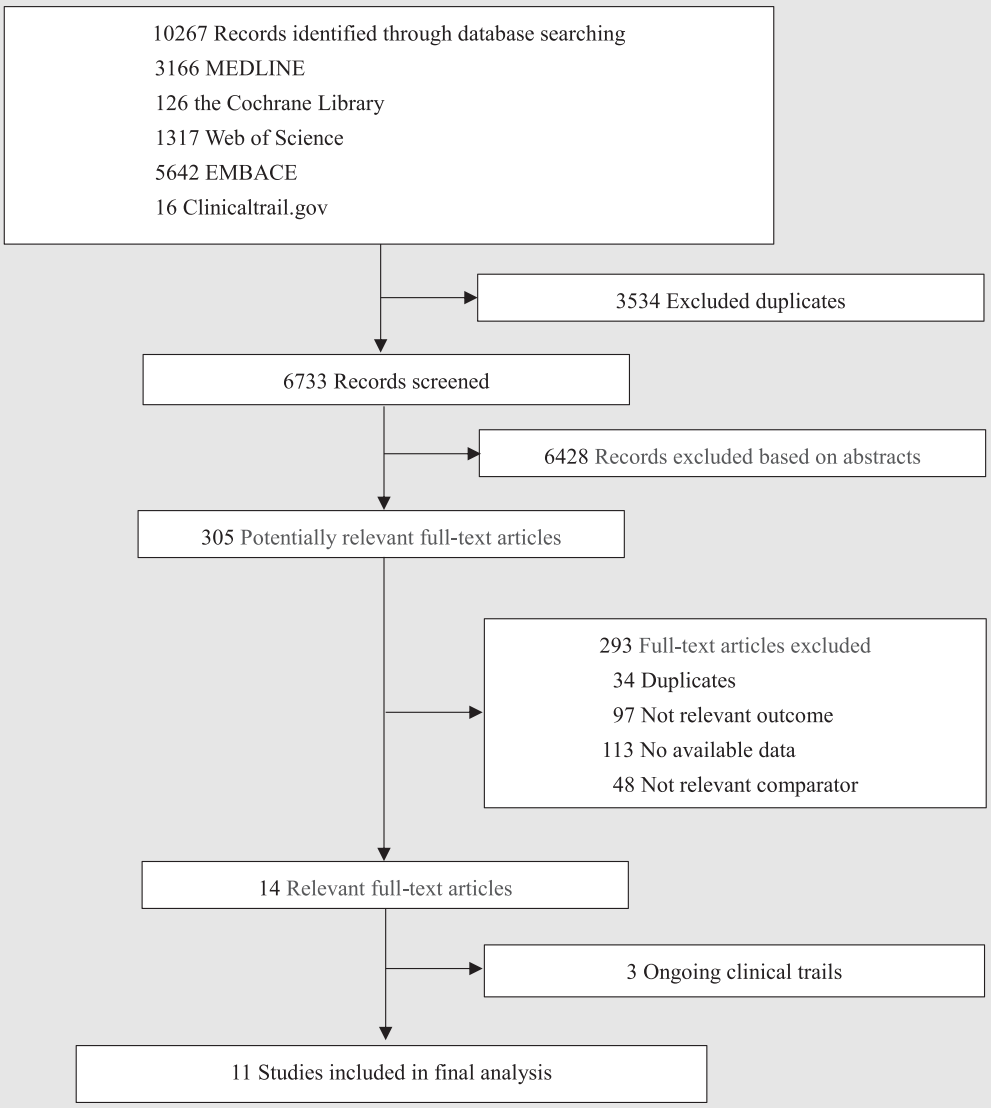
Of the 11 included studies, nine reported data on responder rates, four reported long-term adverse effects, and six reported mortality rates. Six studies compared the efficacy of anti-epileptic drugs as first-line treatment, and five studies compared it as second-line treatment. Most of them reported clinical and demographic characteristics (Table e—16). The average sample size of the studies was 123 participants, ranging from 22 to 413 patients. Approximately half of the sample population was male (579 [61%] of 962), and the mean gestational age was 38.9 weeks (ranging from 25 to 42 weeks). Three studies included seizures caused only by HIE, and five studies included seizures caused by other reasons. Among them, hypoxic-ischemic encephalopathy (519 [53%] of 975) was the predominant reason for seizures, followed by intracranial hemorrhage (129 [13.2%] of 975). Three (30%) studies recruited neonates from the United Kingdom, four (30%) from the United States, and the remaining studies (40%) recruited participants from other countries. In terms of study quality, seven randomized clinical trials, which were assessed by the Cochrane risk-of-bias tool, were rated as having a medium risk of bias (Figure e—1). Of the observation studies, which were assessed by the NOS, five were assessed as medium quality, and two were assessed as high quality (Table e—6). However, in the data analysis, one study was excluded by sensitivity analysis.

3.3. Comparison of effect sizes

Pairwise meta-analysis: We performed pairwise meta-analysis, and the detailed results are given in the supplement (Table e—7). The results indicated that regardless of whether levetiracetam was used as a first-line treatment or second-line treatment, there was evidence suggesting that phenobarbital was more efficacious than phenytoin (OR 1.236 (95% CI 0.63, 2.42)) with heterogeneity (I-squared = 0.00%; P = 0.718) as a first-line treatment. Phenobarbital was more efficacious than levetiracetam (OR 1.248 (95% CI 0.49, 2.23)). It also supports that lidocaine had more control in clinical or electrographic seizures compared with midazolam (OR 1.72 (95% CI 0.99 to 2.96)), which does not have significant heterogeneity (I-squared = 0.00%; P = 0.836) as a second-line treatment. Regarding the rate of long-term adverse effects (Table e—8), the pairwise meta-analysis indicated that neonates receiving phenobarbital had a higher risk of adverse effects than those receiving levetiracetam (OR 1.94 (95% CI 1.19 to 3.17)). Similarly, for mortality rate (Table e—9), it also suggested that a higher rate was observed in the infants who received phenobarbital compared with phenytoin (OR 5.57 (95% CI 1.41 to 21.99)) and levetiracetam (OR 1.72 (95% CI 1.06 to 2.77)) as a first-line treatment. No matter the primary endpoint or secondary endpoints, no evidence of significant heterogeneity in efficacy (I-squared = 0.0%; P < 0.05) or safety (I-squared = 0.0%; P < 0.05) was detected in different trials of the same drug.

Network meta-analysis: Figure e—12 displays the network of the first-line conforming comparisons for efficacy. Fig. 1 displays the network of the second-line conforming comparisons for efficacy. The diagrammatic presentation of the other networks is shown in the Supplement (Figure e—2, Figure e—3, Figure e—4). The results of the network meta-analysis using random effects for

Table 1 Flow diagram of the literature search and trial selection process.



the primary outcomes are given in Table 2 and Table 3. For the efficacy endpoint, when levetiracetam was used as a first-line drug, phenobarbital was better than levetiracetam (OR 1.81 (95% CI 1.21,15.41)) and phenytoin (OR 1.33 (95% CI 1.20–9.00)). Despite being used as a second-line drug, it was also more efficacious than phenytoin (OR 2.18 (95% CI 0.40–11.87)). Lidocaine was significantly more effective than midazolam (OR 2.21 (95% CI 0.37,13.20)) as a second-line treatment. In terms of long-term adverse effects, phenobarbital was associated with a significantly increased risk compared with levetiracetam (OR 1.94 (95% CI 1.19–3.17)), whereas there was a significantly decreased risk compared with midazolam (OR 0.29 (95% CI 0.02–3.67)). Midazolam had a higher risk of long-term adverse effects than levetiracetam (OR 8.58 (95% CI 1.19–62.11)). Regarding the mortality rate (Tables 2 and 3), there was significant evidence that neonates who received levetiracetam as a first-line or second-line drug had a lower risk of mortality than those who received phenobarbital (OR 0.61 (95% CI 0.38–0.99)), whereas neonates who received levetiracetam had a higher risk of mortality than those who received phenytoin (OR 2.54 (95% CI 0.69–9.44)). The I-squared was 35.1% for efficacy and 67.0% for mortality rate as a first-line treatment and 35.4% for efficacy and 49.8% for mortality rate as a second-line treatment. Tests of inconsistency indicated that in the closed loops, there was no significant inconsistency for long-term adverse effects (Figure e–5) or mortality rate (Figure e–6). The test of inconsistency using the node-splitting model showed no differences between comparisons in efficacy outcome (Table e–10), long-term adverse effects and mortality rate (Table e–11, Table e–12). The comparison-adjusted funnel plots for primary or secondary outcomes showed no obvious publication bias (Figures e–7, e–8, e–9, e–10, e–11). The ranking of each anti-epileptic drug based on SUCRAs is summarized in the supplement (Table e–13, e–14). For the first-line drugs, phenobarbital (66.1%) had the highest SUCRA ranking of efficacy. For the second-line drugs,

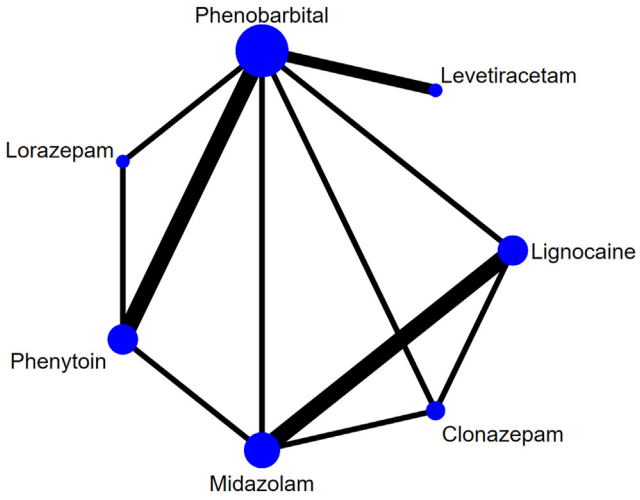


Figure 1 Network of eligible comparisons for efficacy of the second-line anti-epileptic drugs. The width of the lines represents the number of studies comparing each pair of treatments. Furthermore, the size of every circle represents the number of assigned participants.

Table 2 Network meta-analysis of the efficacy and mortality rate of first-line drugs.

Phenobarbital	5.57 (0.50,61.65)	1.83 (1.10,10.42)
1.33 (1.20,9.00)	Phenytoin	0.19 (0.01,5.21)
1.81 (1.21,15.41)	1.36 (0.08,23.97)	Levetiracetam

Comparisons should be read from left to right. The efficacy and the mortality rate are located at the intersection of the column-defining treatment and the row-defining treatment. [a] The drug was used as first-line treatment. For efficacy, an OR above 1 favors column-defining treatment. For the mortality rate, an OR below 1 favors row-defining treatment. To obtain ORs for comparisons in the opposing direction, reciprocals should be taken. Significant results are in bold.

midazolam (80.9%) had the highest SUCRA ranking, and phenytoin (28.6%) had the lowest ranking. However, for the mortality rate, phenytoin was the best drug, regardless of whether it was used as a first-line (11.8%) or second-line (11.9%) drug.

4. Discussion

This is the first network meta-analysis that provides the most comprehensive analysis of data for currently available anti-epileptic drugs for neonates with seizures. According to the data, we found that phenobarbital was more effective than levetiracetam and phenytoin as a first-line treatment. When phenobarbital was used as a second-line drug, it was also more efficacious than any other drug. At the same time, midazolam also showed a better effect on controlling seizures than lidocaine. In terms of secondary outcome, levetiracetam has a lower risk of long-term adverse effects for neonates than phenobarbital. However, these findings are limited not only by the indeterminacy among these estimates but also by the low quality of the included articles. Moreover, risk of bias in individual studies, poor methodology and different types of studies are significant factors that should be considered when explicating the results of this meta-analysis.

Our study has some strengths. First, using network meta-analysis methods, we can compare drugs with each other to provide a hierarchy of the treatments based on efficiency and safety (according to the SUCRA curves),[10] which has not been done before in previous studies. Second, we not only compared the efficacy of first-line anti-epileptic drugs but also compared the efficacy of second-line anti-epileptic drugs. As all the articles included in the analysis were fully published, the risk of heterogeneity was greatly decreased. Moreover, our study may be the first to comprehensively compare and rank the efficacy of anti-epileptic drugs using SUCRA curves.[35,36]

Table 3 Network meta-analysis of the efficacy and mortality rate of second-line drugs.

Phenobarbital[a]	4.14 (1.22,14.08)	1.63 (1.02,2.61)	2.00 (0.69,5.83)	1.27 (0.26,6.33)	1.92 (0.43,8.53)	1.29 (0.10,16.31)
2.18 (0.40,11.87)	Phenytoin[b]	0.39 (0.11,1.46)	0.48 (0.12,1.89)	0.31 (0.05,1.81)	0.46 (0.11,1.99)	0.31 (0.02,4.92)
1.81 (0.25,13.25)	0.83 (0.06,11.31)	Levetiracetam	1.23 (0.38,3.96)	0.78 (0.15,4.16)	1.18 (0.25,5.64)	0.79 (0.06,10.46)
0.60 (0.05,7.63)	0.27 (0.02,3.54)	1.92 (0.43,8.53)	Lorazepam[b]	0.63 (0.10,4.10)	0.96 (0.17,5.35)	0.64 (0.04,9.96)
0.34 (0.03,4.37)	0.15 (0.01,2.53)	1.29 (0.10,16.31)	0.57 (0.02,18.81)	Lidocaine[b]	1.51 (0.34,6.68)	1.01 (0.06,16.80)
0.74 (0.06,9.18)	0.34 (0.02,4.81)	0.41 (0.02,10.16)	1.25 (0.04,38.48)	**2.21 (0.37,13.20)**	Midazolam[b]	0.67 (0.04,10.91)
3.75 (0.07,198.53)	1.72 (0.03,116.93)	2.07 (0.02,175.94)	6.29 (0.06,674.76)	11.12 (0.20,623.69)	5.04 (0.08,299.71)	Clonazepam[b]

Comparisons should be read from left to right. The efficacy and the mortality rate are located at the intersection of the column-defining treatment and the row-defining treatment.
[a] The drug was used as first-line treatment.
[b] The drug was used as second-line treatment. For efficacy, an OR above 1 favors column-defining treatment. For the mortality rate, an OR below 1 favors row-defining treatment. To obtain ORs for comparisons in the opposing direction, reciprocals should be taken. Significant results are in bold.

This study also has some limitations. First, there was a dearth of published, randomized clinical trials that compared AEDs with each other, so not only RCTs but also observation studies were included, resulting in the low quality of this study. There are multifaceted reasons for the lack of clinical trials, such as expense, the need for cooperation between multiple neonatal centers to ensure adequate statistical power and the difficulty of enrolling neonates in clinical trials of anti-epileptic drugs. A recently published article on the medical treatment of neonatal seizures[17] recommends that more randomized, double-blind, placebo or active controlled trials be performed to provide evidence for further study. Second, in the network, due to data limitations, we could not compare the inconsistency between direct and indirect results of efficacy and mortality for first-line drugs, which makes our results equivocal. The American Clinical Neurophysiology Society[29] divided neonatal seizures into three types: (i) clinical-only seizures, (ii) electroclinical seizures and (iii) EEG-only seizures. However, in this study, some included studies focused entirely on clinical seizures or EEG seizures, whereas others had to have both clinical and electrical seizures (utilizing video EEG or aEEG) controlled. Such heterogeneity might appear in forest plot analyses and may not only reduce the effect of the results but also restrict universalization of the findings. Hence, even though we made indirect comparisons among the seven AEDs using suitable statistical approaches, the results need to be explained carefully. Third, the control of seizures depends to a large extent on the underlying etiology, which may not be possible unless the underlying defect or deficiency is addressed. However, the included studies differed in the characteristics of neonates, such as the pathogeny or type of seizure. Finally, previous studies showed that changes in energy metabolism occurred within 5 min after the onset of seizures;[30] thus, individual trials only provided information on a short period of time (typically 5 minutes-24 h). However, to be more accurate, the studies should take a longer time into consideration. Based on expert opinion, the proposed seizure-free time is 72 h,[15,16] and even less information is available about the time interval between discontinuing AEDs and achieving seizure control.

In the absence of randomized controlled trials (RCTs), the Queensland clinical guidelines of neonatal seizures recommend phenobarbital as the first-line drug, considering the available aspects, including efficacy, toxicity, side effects and anticipated rapidity of response. There are several meta-analyses and reviews related to this question. Slaughter LA[15] systematically reviewed studies, including observational investigations and trials, to determine the most effective medication(s) for neonatal seizures. Considering PB's historical precedence for neonatal seizures, the review, even though only one RCT of first-line therapy was included, also recommends phenobarbital as a first-line treatment. The guidelines on neonatal seizures published in the WHO[15] also reported that phenobarbital should be used as the first-line drug for neonatal seizures. Booth D[31] only included two published RCTs that compared phenobarbital versus phenytoin and lidocaine versus midazolam. They found that phenobarbital and phenytoin were similarly effective in controlling seizures. Compared with lidocaine, midazolam tends to be more effective. Lena HMW[32] reported a systematic review of the current management strategies of neonatal seizures by analyzing all surveys published between 2000 and 2012. They found that phenobarbital was the most selected first-line drug for neonatal seizures in pediatric neurologists and neonatologists. When this treatment fails, neonatologists prefer to use a high dose of PB, whereas pediatric neurologists seem to favor other AEDs, such as topiramate and levetiracetam. Phenytoin is the second choice of anti-epileptic therapy, and its combinative efficiency was more than 60%, even though it has potential neurotoxicity and limited efficacy. In recent years, new agents, such as topiramate and levetiracetam, have also often been used despite their efficacy, side effect profiles and pharmacokinetic data being limited.[34] In addition, more studies point out that levetiracetam, one of the FDA-approved AEDs for one-month-old children, is a good choice for neonatal seizures.[10] Falsaperla R[35] performed a prospective study, finding that the patients who received levetiracetam as a first-line treatment all responded to it with a range of seizure cessation periods (from 24 h to 15 days). Rao LM[28] retrospectively compared the efficacy of levetiracetam and phenobarbital for newborns with seizures confirmed by continuous video-electroencephalogram (VEEG). They suggested that levetiracetam is a viable alternative to phenobarbital in the treatment of neonatal seizures caused by HIE. Ahmad KA did a survey and reported that phenobarbital exposure decreased from 99 to 96%, phenytoin exposure declined from 15 to 11% and levetiracetam exposure increased from 1.4 to 14% from 2005 to 2006 to 2013–2014. Levetiracetam is widely used despite limited evidence that may be related to its ease of use, its safety profile in older children and its lack of sedating effects and electroencephalogram depression. In addition, three ongoing RCTs are trying to compare the efficacy between levetiracetam and phenobarbital, which means that it is gradually receiving more attention.

5. Conclusions

Due to the lack of more reliable data, we still recommend phenobarbital as the first-line treatment for neonatal seizures, considering available aspects including efficacy, toxicity and side effects. Moreover, regardless of the efficacy or mortality rate, phenytoin was better than other drugs as the first-line drug, except phenobarbital. In addition, there is a tendency for levetiracetam to be an effective second-line treatment for neonatal seizures after failure of first-line drugs. In summary, because of the lack of adequate RCTs and other aspects, the quality of our study is low. Therefore, more standardized, larger, and long-term studies are required.[17]

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Author contributions

Dr Xu and Mr. Li conceptualized and designed the study, analyzed the data, drafting and revision of manuscript. Ms. Qiao and Mr. Cui conceptualized and designed the study, designed the data collection instruments. Mr. Zhao, Ms. Qiao and Dr Xu designed the data collection instruments, collected data, carried out the initial analyses. Dr Chen and Ms. Miao conceptualized and designed the study, coordinated, and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2021.06.005.