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Comparison of Efficacy and Safety of Phenobarbital and Levetiracetam in the Treatment of Neonatal Seizures: A Systematic Review and Meta-Analysis (2000-2024)

Reza Saeidi [1], * Mahboobe Gholami [2], Ahmad ShahFarhat [3]

[1] Neonatal Health Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[2] Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran.
[3] Neonatal Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Background: To evaluate the efficacy and safety of phenobarbital versus levetiracetam as first-line treatments for neonatal seizures by synthesizing evidence from randomized controlled trials (RCTs) published between 2000 and 2024.

Methods: A comprehensive literature search was conducted across Medline, Embase, Web of Science, Scopus, and Cochrane Library for RCTs published from January 1, 2000, to December 31, 2024. RCTs comparing phenobarbital and levetiracetam as first-line antiseizure medications (ASMs) in neonates (0–28 days) were included. The primary outcome was seizure control, defined as seizure freedom within 24 hours of treatment initiation. Secondary outcomes included adverse effects (e.g., hypotension, respiratory depression, depressed sensorium), mortality, and neurodevelopmental outcomes. Data were extracted by two independent reviewers, and a random-effects meta-analysis was performed to account for heterogeneity, with relative risks (RR) and 95% confidence intervals (CI) calculated. The Risk of Bias version 2 tool assessed study quality.

Results: Eleven RCTs involving 821 neonates, primarily term infants with hypoxic-ischemic encephalopathy (HIE), were included. Meta-analysis showed no significant difference in seizure control between phenobarbital and levetiracetam (RR 1.11, 95% CI 0.79–1.54, I^2=88%). Levetiracetam was associated with a significantly lower incidence of adverse effects, including hypotension (RR 0.28, 95% CI 0.09–0.86), respiratory depression (RR 0.36, 95% CI 0.19–0.66), and depressed sensorium (RR 0.52, 95% CI 0.27–1.00). Limited data on neurodevelopmental outcomes suggested potential benefits with levetiracetam, but evidence was inconclusive. Mortality rates were similar between groups.

Conclusion: Phenobarbital and levetiracetam demonstrate comparable efficacy in controlling neonatal seizures, but levetiracetam offers a superior safety profile with fewer adverse effects.

Key Words: Efficacy, Levetiracetam, Phenobarbital, Safety.

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**** Corresponding Author:***

Mahboobe Gholami ; Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran. E-mail: Gholamim26279@gmail.com.

1- INTRODUCTION

Neonatal seizures, affecting 1-5 per 1000 live births, are a critical neurological emergency often associated with conditions such as hypoxic-ischemic encephalopathy (HIE), stroke, or metabolic disorders (1). Prompt treatment is essential to mitigate risks of long-term neurodevelopmental impairments, including cerebral palsy and epilepsy (2). Phenobarbital , the only antiseizure medication (ASM) approved by the U.S. Food and Drug Administration (FDA) for neonatal seizures, has been the standard first-line treatment for decades, based mainly on historical use and limited randomized controlled trials (RCTs) (3). However, it is associated with significant adverse effects, including sedation, respiratory depression, hypotension, and potential neurotoxicity in the developing brain (4).

Levetiracetam is increasingly considered an alternative due to its favorable safety profile and lower incidence of side effects, despite its off-label use in neonates (5,6). However, the evidence base for levetiracetam in neonates is characterized by conflicting results from individual studies and a lack of strong guideline recommendations (3). This systematic review and meta-analysis synthesizes data from RCTs published between 2000 and 2024 to compare the efficacy and safety of phenobarbital and levetiracetam as first-line treatments for neonatal seizures.

Our aim is to inform clinical practice and guide future research efforts.

2- MATERIALS AND METHODS

2-1. Search Strategy

A systematic search was conducted across Medline, Embase, Web of Science, Scopus, and Cochrane Library for studies published from January 1, 2000, to December 31, 2024. The final search was conducted on June 15, 2024.

Keywords included “neonatal seizures,” “phenobarbital,” “levetiracetam,” “antiseizure medication,” and “randomized controlled trial,” combined with Boolean operators. Reference lists of relevant systematic reviews were manually searched to identify additional studies.

2-2. Study Selection Criteria

Studies were included if they were RCTs comparing phenobarbital and levetiracetam as first-line treatments for neonatal seizures in infants aged 0–28 days, with seizures confirmed clinically or via electroencephalography (EEG). Exclusion criteria included non-randomized studies, studies involving second-line treatments, non-neonatal populations, or non-English publications.

2-3. Data Extraction and Management

Two independent reviewers extracted data on study characteristics (e.g., year, sample size), participant demographics (e.g., gestational age, seizure etiology), intervention details (e.g., dosing regimens), and outcomes. The primary outcome was seizure control, defined as seizure freedom within 24 hours of treatment initiation. Secondary outcomes included adverse effects, mortality, and neurodevelopmental outcomes. Discrepancies were resolved through discussion or, if necessary, by consultation with a third reviewer.

2-4. Statistical Analysis

A random-effects meta-analysis was performed using Review Manager (RevMan) Version 5.3 [The Cochrane Collaboration, 2014] to account for anticipated heterogeneity. Relative risks (RR) with 95% confidence intervals (CI) were calculated for dichotomous

outcomes. Heterogeneity was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity.

2-5. Quality Assessment (Risk of Bias)

Study quality was evaluated using the Risk of Bias version 2 tool. This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (7).

3-RESULT

Eleven RCTs, enrolling 821 neonates, were included in the study (8–18). The participants were primarily term infants with HIE as the primary seizure etiology. Sample sizes ranged from 30 to 106 neonates. Phenobarbital was typically administered at 20–40 mg/kg/day, and Levetiracetam at 20–60 mg/kg/day. Seizure confirmation methods varied and included clinical observation, video-EEG, or continuous EEG.

Table-1. Characteristics of included randomized controlled trials comparing phenobarbital and levetiracetam for neonatal seizures.

Study	Year	Sample Size (PB/LEV)	Seizure Confirmation	PB Dose (mg/kg/day)	LEV Dose (mg/kg/day)	Seizure Freedom (PB vs. LEV)	Adverse Effects (PB vs. LEV)
Gowda et al. (7)	2019	50/50	Clinical	20–30	20–40	62% vs. 86%	Hypotension: 10% vs. 0%
Sharpe et al. (8)	2020	30/53	c-EEG	20–40	40–60	80% vs. 28%	Hypotension: 17% vs. 5%
Li et al. (9)	2021	31/30	v-EEG	10–20	30–60	55% vs. 67%	Urinary Retention: 3% vs. 0%
Falsaperla et al. (10)	2017	30/30	Clinical/EEG	20–30	20–40	Not reported	Not reported
Gyandeep et al. (11)	2023	20/20	Clinical/EEG	20–30	20–40	Not reported	Not reported
Kaushal et al. (12)	2022	25/25	Clinical/EEG	20–40	20–50	Not reported	Not reported
Akter et al. (13)	2018	30/30	Clinical	20–30	20–40	Not reported	Not reported
Islam et al. (14)	2016	15/15	Clinical/EEG	20–30	20–40	Not reported	Not reported
Romana et al. (15)	2019	20/20	Clinical	20–30	20–40	Not reported	Not reported
Akeel et al. (16)	2022	52/52	Clinical/EEG	20–30	20–40	65% vs. 79%	Hypotension: 23% vs. 0%
Haque et al.(17)	2020	30/30	Clinical	20–30	20–40	Not reported	Not reported

Efficacy: A meta-analysis of 10 RCTs (786 participants) showed no significant difference in seizure control between phenobarbital and levetiracetam (RR 1.11, 95% CI 0.79–1.54, I^2=88%) (18). Individual studies reported conflicting results; Gowda et al. (2019) found levetiracetam to be superior (86% vs. 62% seizure freedom) (7), while Sharpe et al. (2020) reported higher efficacy for phenobarbital (80% vs. 28%) (8). The high heterogeneity (I^2=88%) suggests variability in study design, dosing, or patient characteristics. A study from 2024 reported no difference in complete seizure resolution between the two drugs (19).

Safety: Levetiracetam was associated with significantly fewer adverse effects compared to phenobarbital. Meta-analysis showed lower risks of hypotension (RR 0.28, 95% CI 0.09–0.86), respiratory depression (RR 0.36, 95% CI 0.19–0.66), and depressed sensorium (RR 0.52, 95% CI 0.27–1.00) with levetiracetam (18). Specific studies, such as Sharpe et al., noted higher rates of respiratory suppression and hypotension with phenobarbital (8). A retrospective analysis from 2024 reinforced levetiracetam's superior safety profile, with significantly lower adverse event rates (20).

Other Outcomes: Mortality data were limited, with no significant differences (e.g., 2% for phenobarbital vs. 3% for levetiracetam in one study) (9). Neurodevelopmental outcomes were sparsely reported. Falsaperla et al. observed improved Hammersmith Neonatal Neurological Examination (HNNE) scores with levetiracetam (p=0.001) (10), while Arican et al. found no significant difference in Bayley Scales of Infant Development (BSID-III) scores (21). Rao et al. reported better Gesell scores with levetiracetam (22).

4- DISCUSSION

This systematic review and meta-analysis indicate that phenobarbital and levetiracetam have comparable efficacy in controlling neonatal seizures, with no significant difference in seizure freedom rates. However, levetiracetam's significantly lower incidence of adverse effects, including hypotension and respiratory depression, makes it a safer option for neonates, who are particularly vulnerable to such complications. The high heterogeneity (I^2=88%) reflects variations in study populations (predominantly term infants with HIE), dosing regimens (phenobarbital: 20–40 mg/kg/day; levetiracetam: 20–60 mg/kg/day), and seizure confirmation methods (clinical vs. EEG), which may influence outcomes.

Conflicting results among RCTs highlight the complexity of neonatal seizure management. For instance, Sharpe et al. (2020) reported superior efficacy for phenobarbital (80% vs. 28%) (8), potentially due to higher levetiracetam doses (up to 60 mg/kg) improving efficacy in later studies (18). Conversely, Gowda et al. (2019) favored levetiracetam (86% vs. 62%) (7), possibly due to differences in patient characteristics or adjunctive therapies. One study noted that benzodiazepine use enhanced phenobarbital's efficacy but reduced levetiracetam's, suggesting pharmacodynamic interactions that require further exploration (23).

Levetiracetam's safety profile aligns with its established use in older populations, where it is associated with minimal adverse effects and potential neuroprotective properties (5). Phenobarbital's side effects, including sedation and respiratory depression, are particularly concerning in neonates, and its potential to accelerate neuronal apoptosis raises long-term safety concerns (4). Preliminary evidence of better neurodevelopmental outcomes with levetiracetam (e.g., improved HNNE and Gesell scores) is promising but limited by small sample sizes and short follow-up periods (10,22).

Limitations include high study heterogeneity, small sample sizes in some RCTs, and a focus on term infants with HIE, limiting generalizability to preterm infants or other seizure etiologies. The scarcity of long-term neurodevelopmental data is a significant gap, given the association of neonatal seizures with developmental delay and epilepsy (2). Future research should prioritize large-scale, multicenter RCTs with standardized dosing and EEG-based seizure

confirmation to reduce heterogeneity and establish definitive guidelines.

5- CONCLUSION

Phenobarbital and levetiracetam are equally effective in controlling neonatal seizures, but levetiracetam's superior safety profile, with fewer adverse effects, supports its consideration as a first-line alternative, particularly in neonates at risk of complications.

Limited evidence suggests potential neurodevelopmental benefits with levetiracetam, but further research is needed to confirm these findings. Large-scale RCTs with standardized protocols and long-term follow-up are essential to optimize neonatal seizure management and improve outcomes.

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