ORIGINAL ARTICLE

Comparing the Effectiveness and Safety of Intravenous Levetiracetam and Phenobarbital as First-Line Therapies for Neonatal Seizures: A Randomized Clinical Trial

Nahideh Khosroshahi, MD; Kamyar Kamrani, MD; Muhammadhosein Moradi, MD; Parisa Sadeghirad, MD; Ayda Khabazi Oskouie, MD

[1] Deviation of Pediatric Neurology, Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2] Deviation of Neonatology, Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3] Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran

Keywords:

Neonatal seizure
Phenobarbital
Levetiracetam
Initial therapy

Received:
05- May -2024
Accepted:
11- Sep-2024
Published:
11- Mar-2025

ABSTRACT

Objectives

This randomized clinical trial aims to evaluate and compare phenobarbital and levetiracetam effectiveness and safety in controlling neonatal seizures as first-line therapeutic options.

Materials & Methods

Neonates with seizure manifestations presenting to the Bahrami Hospital from March 2020 to March 2022 were enrolled in this study. Patients' data were recorded, including demographic findings, anthropometric measurements, birth characteristics, and laboratory findings. Patients were randomly divided into the phenobarbital and levetiracetam treatment groups. Outcomes defined as adverse effects, response to medication, time to start enteral feeding, and length of hospital stay were compared between the two treatment groups.

Results

The current study comprises 44 neonates divided into phenobarbital and levetiracetam groups. Seizure control among the two groups was not significantly different, with levetiracetam and phenobarbital groups showing seizure control of 68.2% and 59.1%, respectively. Moreover, no significant difference was observed regarding the duration of hospitalization and time to initiate feeding. No adverse effect was reported in either group.

Conclusion

This study showed no significant difference between levetiracetam and phenobarbital for neonatal seizure control.

How to cite this article: Khosroshahi N, Kamrani K, Moradi M, Sadeghirad P, Khabazi Oskouie A. Comparing the Effectiveness and Safety of Intravenous Levetiracetam and Phenobarbital as First-Line Therapies for Neonatal Seizures: A Randomized Clinical Trial. Iran J Child Neurol. 2025; 19(2): 65-75. https://doi.org/10.22037/ijcn.v19i2.45234

Corresponding Author: Khabazi Oskouie A, MD. Department of Pediatrics, Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran. Email: Aydakh334@yahoo.com

© 2025 The Authors. Published by Shahid Beheshti University of Medical Sciences.
This work is published as an open access article distributed under the terms of the Creative Commons Attribution 4.0 License. Non-commercial uses of the work are permitted, provided the original work is properly cited.

Introduction

Neonatal seizures, defined by hypersynchronous discharges of the central nervous system (CNS), occur in infants under 28 days of age for term neonates or infants born under the gestational age of 44 weeks in preterm neonates (1-3). Neonatal seizures are the most common neonatal CNS complication (4), affecting approximately 1.5 to 3.5 per 1000 neonates, with a higher incidence of 130 cases per 1000 neonates in preterm neonates (1, 4). Identifiable causes account for 85% of seizures, with hypoxic-ischemic encephalopathy (HIE) and asphyxia being the most common predisposing factors and accounting for 50%-75% in some studies, while neonatal epileptic syndromes account for the remaining 15% (4, 5). Prolonged and uncontrolled seizures can induce hypoxic and ischemic changes, potentially leading to neural damage (6). Thus, simultaneous seizure control and detection of the underlying causes is imperative (7).

Phenobarbital is the first-line therapeutic choice for neonatal seizures, with a demonstrated efficacy rate of 33%-77%. The mechanism of action comprises neural membrane hyperpolarization through modulating the α-subunit of the Gamma Amino Butyric Acid receptors (8-10), increasing the seizure threshold and preventing further seizure exacerbation (11). However, despite its broad use and extensive administration experience, safety concerns have been raised regarding the continuation of phenobarbital as the first-line therapy for neonatal seizures (12). Side effects, including sedation, bradycardia, and respiratory depression, have been mentioned. Animal studies in mouse models have also suggested long-term brain neural cell apoptosis induction in animals receiving phenobarbital (13). As a result, the use of other anti-seizure medications has been under evaluation.

Levetiracetam inhibits N-type voltage-gated calcium channels and modifies glutamate release by affecting the glycoprotein 2A of the synapsis vesicles (14-16), and since 2012, has been approved by the Food and Drug Administration as an adjuvant therapy for seizure control in patients one month of age and older (17). Levetiracetam has received considerable attention due to its fewer side effects, renal excretion, non-hepatic metabolism, and effectiveness in older children (5, 18). A recent meta-analysis by Qiao et al.(19), including ten articles, reported no superior effectiveness for levetiracetam. However, it demonstrated significantly lower adverse effects. Hence, this study compares the effectiveness and safety of intravenous levetiracetam and phenobarbital as first-line medications in controlling neonatal seizures.

Materials & Methods

Study design and population

This study was an open-label parallel randomized clinical trial conducted in Bahrami Children's Hospital neonatal intensive care unit (NICU) from March 2020 to March 2022. Neonates under 28 days of age who presented to the emergency department with neonatal seizure manifestations were included in this study. Neonatal seizure manifestations were detected by at least two trained medical staff, including neonatologists and experienced NICU nurses, based on the definition detailed below. Neonates with renal and hepatic dysfunction (due to the impact on the drugs' metabolism), congenital syndromes, breastfed infants with mothers on anti-seizure medications, and those without parental or guardians' consent for participation were excluded from this study.

Data extraction

Patients' data, including age, sex, gestational age, method of delivery, first- and fifth-minute APGAR scores, birth weight, length, and head circumference, were obtained based on the birth certificates. Patients' weight, height, and head circumference were measured, and a comprehensive neurologic examination was conducted. Laboratory investigations of total and indirect bilirubin, serum glucose, calcium, magnesium, sodium, potassium, urea, creatinine, and phosphorus levels were evaluated. The duration of hospitalization and time to initiate enteral feeding were recorded accordingly.

Study protocol

Following the diagnosis of neonatal seizures, the patients were placed under cardiac monitoring and pulse oximetry, and conservative therapeutic approaches for oxygenation, lateral decubitus placement, and intravascular rehydration were initiated. The patients were put on a "nothing by mouth" (NPO) diet until their seizures were under control and the patient's condition stabilized. Blood samples were taken before the medication initiation, and brain ultrasonography and lumbar puncture were performed. Following the implementation of the inclusion and exclusion criteria, patients were randomly assigned to each treatment group. Patients in the phenobarbital group received an initial loading dose of 20mg/kg, followed by a maintenance dose of 5 mg/kg dailyin two separate doses after 24 hours. For the levetiracetam group, an initial dose of 40mg/kg was administered, followed by a maintenance dose of 40mg/kg daily within two separate doses after 24 hours until discontinuation (20).

For patients with uncontrolled or repeated seizures, the patients were managed with the addition of a phenobarbital bolus dose of 20mg/kg and upscaling up to 40mg/kg daily in the phenobarbital group. If seizures remained uncontrolled, levetiracetam was added to the anti-seizure treatment. For the levetiracetam group, phenobarbital was added. If the seizures were not controlled, second-line anti-seizure medications, including phenytoin, were administered according to the guidelines. Seizure control was evaluated in 24-hour intervals.

Outcomes

Seizure control was the primary outcome, defined as the absence of clinical seizures following medication administration within the first 24 hours of hospitalization. It was assessed by trained medical staff based on the presence of neonatal seizure manifestation. Secondary outcomes were defined as the length of the hospital stay and the time to start enteral feeding.

Sample size

According to the Maitre et al.'s (21) study, the sample size was determined as a minimum of 12 patients in each treatment group, with an α=0.05, β=0.1, p_1=25%, p_2=75%, a statistical power of 80%, and a 95% confidence interval.

$$n_1 = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \frac{p1(1-p1)+p2(1-p2)}{(p1-p2)^2}$$

Randomization

The Block randomization method used computer-generated 4- and 6-allele blocks to randomly allocate patients into two groups, each consisting of 22. One group received the standard-of-care phenobarbital medication, and the second received levetiracetam.

Definitions

Neonatal seizures: Neonatal seizures are defined as the presence of focal or multifocal clonic, tonic, or myoclonic movements, darting tongue movements, pedaling, rowing, bicycling, apnea, and abnormal eye movement detected by at least two experienced NICU staff.

APGAR: The APGAR mnemonic serves as a helpful tool in outlining the elements of the score: appearance, pulse, grimace, activity, and respiration. This scoring system assesses newborns right after delivery and during resuscitation efforts (22).

Uncontrolled Seizure: Seizures repeating within 24 hours after the initiation of the anti-seizure medication were considered uncontrolled seizures.

Abnormal Brain Ultrasonography: Presence of interventricular hemorrhage, germinal matrix hemorrhage, or structural anomalies in brain ultrasonography.

Abnormal Lumbar Puncture: Presence of cloudy or bloody appearance, Red Blood Cells, White Blood Cells (Pleocytosis), increased protein levels, and low glucose level in the cerebrospinal fluid (CSF)

Ethical consideration

Written informed consent was obtained from the patients' parents/guardians. All procedures performed in this study involving human participants were under the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and were approved by the Research Ethics Committee of the Faculty of Medicine, Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.747). This study was registered, reviewed, and approved by the Iranian Registry of Clinical Trials (IRCT20220410054471N1).

Statistical analysis

All Statistical analyses were performed using the statistical packages for social studies (SPSS) version 27 (IBM, Chicago, USA). Means, standard deviations, and median and interquartile ranges were used to describe quantitative data. Qualitative data are presented as counts and percentages. Comparison between the two groups was performed using independent samples T-test, Wilcoxon Rank-Sum test, and Pearson's Chi-Square test. A non-parametric ANCOVA test (Quad's) was used to adjust for gestational age, hyperbilirubinemia, birth weight, birth head circumference, and serum calcium level. A p-value<0.05 was considered significant.

Results

Baseline characteristics

Forty-four participants were enrolled in this study, distributed evenly between two groups receiving levetiracetam or phenobarbital, maintaining a 1:1 ratio. Regrettably, two patients assigned to the levetiracetam group died due to uncontrolled seizures during the study period.

The mean age of patients in the levetiracetam group was 13.04± 12.72 days, while in the phenobarbital group, it was 12.63± 10.53 days. The male participants comprised a more significant portion of the study population, with 63.6% and 59.1% in the levetiracetam and phenobarbital groups, respectively. No statistically significant differences were detected between the two groups regarding age (p=0.962) and gender (p=1.00).

Gestational age in the levetiracetam group averaged 37.00± 2.69 weeks, compared to 38.45± 1.09 weeks in the phenobarbital group,

with levetiracetam participants having a statistically significant lower gestational age (p=0.034). Similarly, the mean birth weight in the levetiracetam group was 2789.32± 657.00 grams, significantly lower than the phenobarbital group's mean of 3189.55± 434.31 grams (p=0.022). Head circumference at birth was 33.36± 2.39 cm in the levetiracetam group and 34.63± 1.33 cm in the phenobarbital group, with the phenobarbital group having statistically significant higher head circumference at birth (p=0.037). Additionally, hyperbilirubinemia was noted in 13 (59.1%) of the levetiracetam group, while four (18.2%) participants in the phenobarbital group exhibited hyperbilirubinemia, indicating a significantly higher incidence in the levetiracetam group (p=0.012). A detailed summary of baseline demographics, birth characteristics, anthropometric measures, and laboratory findings is presented in Table 1.

Table 1. Baseline Characteristics of participants presented in each treatment group

Characteristics	Treatments Groups		p-value[1]
	Levetiracetam (N=22)	Phenobarbital (N=22)	
Demographic Findings			
Age (days)	9.50 (2.87, 26.00)	7.50 (3.00, 23.00)	0.962
Sex, male (%)	14 (63.6)	13 (59.1)	1.00
Consanguinity, Related	6 (27.3)	7 (31.8)	1.00
Birth Findings			
Delivery, Cesarean (%)	16 (72.7)	18 (81.8)	0.721
Gestational Age (Weeks)	38.00 (36.60, 38.78)	38.28 (38.00, 39.00)	0.034*
First minute APGAR	9.00 (8.00, 9.00)	9.00 (7.00, 9.00)	0.253
Fifth minute APGAR	10.00 (8.00, 10.00)	9.50 (9.00, 10.00)	0.795
Birth Weight (gr)	2789.32± 657.00	3189.55± 434.31	0.022*
Birth Height (cm)	48.97± 2.44	50.00± 2.85	0.246
Birth Head Circumference (cm)	33.36± 2.39	34.63± 1.33	0.037*
Hyperbilirubinemia, yes (%)	13 (59.1)	4 (18.2)	0.012*
Anthropometric Findings			
Weight (gr)	2867.00± 715.94	2897.67± 801.44	0.908
Length (cm)	49.20± 2.48	49.00± 1.22	0.869
Head Circumference (cm)	34.12± 2.68	35.50± 1.11	0.213
Laboratory Findings			

Continued Table 1.

Blood Sugar (mg/dL)	81.82± 36.08	79.55± 38.78	0.841
Calcium (mg/dL)	8.85± 1.06	9.37± 0.74	0.070
Magnesium (mg/dL)	3.21± 4.88	2.04± 0.51	0.269
Sodium (mg/dL)	135.27± 6.91	137.00± 7.18	0.421
Potassium (mg/dL)	4.55± 0.70	4.51± 0.67	0.862
Phosphorus (mg/dL)	5.03± 0.87	5.51± 1.11	0.118
Bilirubin Total (mg/dL)	13.68± 5.94	8.05± 3.31	0.023*
Bilirubin Indirect (mg/dL)	0.50 (0.375, 0.650)	0.500 (0.325, 0.725)	0.917

[1]: Independent Sample T test, Wilcoxon Rank-Sum test, *: $p<0.05$

Quantitative data are presented as Mean± Std Dev and Median (IQR)

Qualitative data are presented as count (%)

Outcomes

Seizure control with levetiracetam, employed as a first-line treatment, was evident in 15 (68.2%) participants, while 13 (59.1%) participants in the phenobarbital group achieved similar control. Figure 1 depicts the proportion of seizure control within each treatment group. The mean time to initiate enteral feeding was 2.14± 1.45 days for the levetiracetam group and 2.68± 2.21 days for the phenobarbital group. Moreover, the mean duration of hospital stay was 8.77± 4.02 days for levetiracetam and 14.41± 12.64 days for phenobarbital. No statistically significant differences were observed between the two groups regarding seizure control effectiveness (p=0.755), time to initiate enteral feeding (p=0.643), and length of hospital stay (p=0.106). Additionally, adjusting for gestational age, hyperbilirubinemia, birth weight, head circumference at birth, and serum calcium level revealed no significant differences between the two groups. In the current study, no adverse effects, including hypotension, respiratory depression, bradycardia, or dermatologic reactions, were observed. A comprehensive summary of study outcomes for each treatment group is presented in Table 2.

Discussion

This randomized clinical trial investigates the effectiveness and safety of employing intravenous levetiracetam and phenobarbital as first-line interventions to manage neonatal seizures, irrelevant to the etiology. Due to the emergent nature of neonatal seizures, rapid and safe interventions can significantly improve the prognosis of the patients and prevent its harmful effects. Notably, in this study, no significant difference was discerned in terms of the study end-points between the two groups. Nevertheless, levetiracetam exhibited a non-significantly higher seizure control rate and shorter length of hospital stay compared to the phenobarbital. The present study focused on comparing the effectiveness of two medications as initial therapy, regardless of the underlying etiology of the disease. Sadly, during the study, two patients passed away due

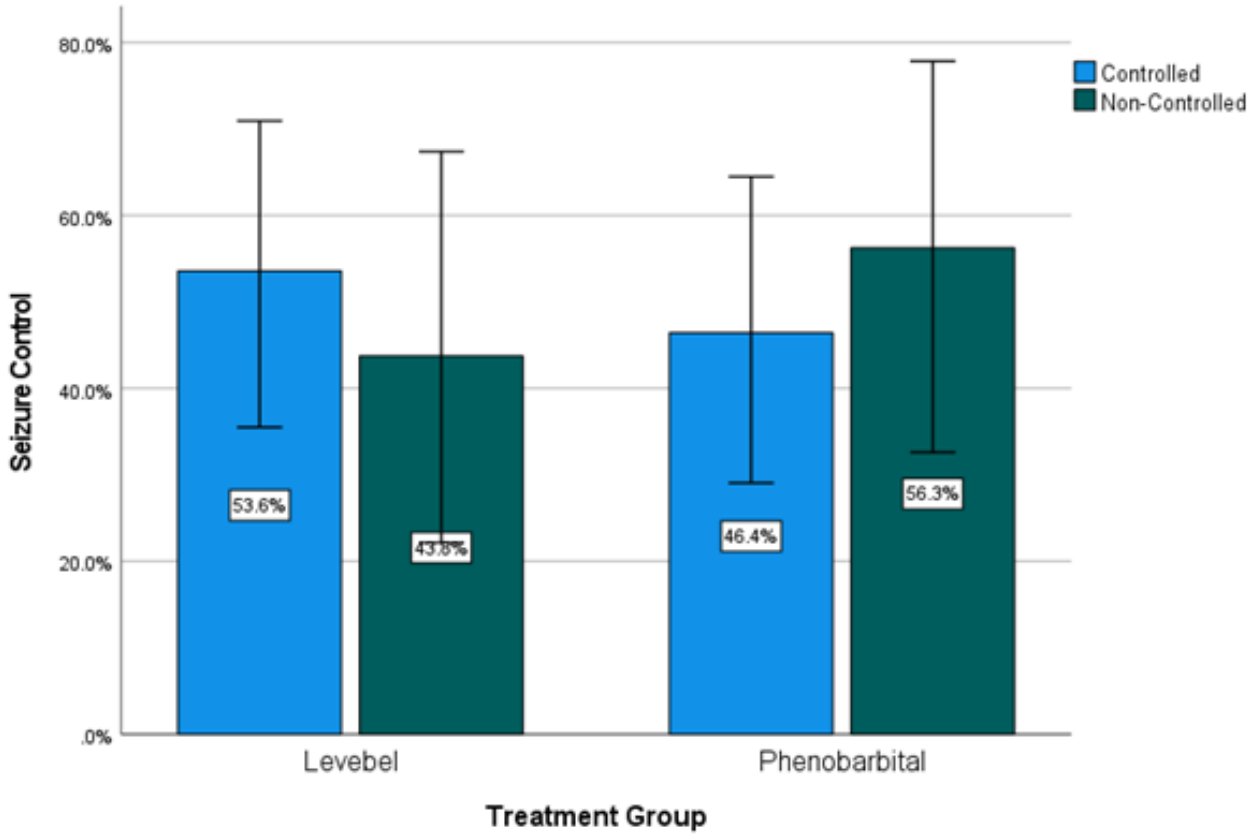

Figure 1. Bar charts with error bars represent seizure control rates in each treatment group; the findings favor higher seizure control rates in the Levebel treatment group

Table 2. Unadjusted and adjusted comparison of patients' outcomes between the treatment groups

Test	Male Average ± STD	Female Average ± STD	P-value	Ages ≤ 6 Average ± STD	Ages ≥ 7 Average ± STD	P-value
WBC (×10^9/L)	9.2 ± 5 0.16	9.9 ± 2.3 0.86	0.27	8.96 ± 4.4 0.57	10.19 ± 3.9 0.68	0.2803
PMN (%)	50.3 ± 16.2 0.2	64.01 ± 15.7 0.1	0.004	52.8 ± 19.37 0.06	58.7 ± 15.5 0.24	0.005
Lymphocytes (%)	39.08 ± 15.6 0.31	28.6 ± 13.4 0.07	0.025	38.6 ± 17.5 0.1	30.9 ± 13.1 0.7	0.041
NLR	1.8 ± 1.4 0.4	3.2 ± 2.7 0.42	0.09	2.22 ± 2.6 0.24	2.5 ± 1.7 0.59	0.12
Platelets (/mcL)	321.9 ± 113.6 0.11	392.9 ± 112.6 0.71	0.08	362.78 ± 116.98 0.66	334.7 ± 125.4 0.11	0.47

Continued Table 2.

ESR (mm/h)	18.8 ± 10.4	30.5 ± 20.05	0.14	21.1 ± 11.4	25.8 ± 20.3	0.15
	0.14	0.99		0.16	0.176	
CSF Sugar (mg/dL)	75.7 ± 17.5	69.3 ± 12.3	0.74	75.1 ± 14.3	71 ± 18.4	0.76
	0.97	0.51		0.93	0.68	
CSF Protein (mg/dL)	31.3 ± 17.8	39.8 ± 19.6	0.75	31.8 ± 17.4	37.8 ± 21.7	0.69
	0.85	0.69		0.25	0.78	
CSF Whites (mg/100 mL)	2.04 ± 5.9	17.1 ± 40.2	0.18	3.6 ± 8.1	12.6 ± 36.9	0.14
	0.83	0.37		0.36	0.09	
CSF NLR	0.01 ± 0.03	0.3 ± 0.6	0.06	0.18 ± 0.5	0.06 ± 0.16	0.14
	0.68	0.24		0.17	0.36	

to refractory seizures and related complications, including aspiration and hypothermia. In both cases, there was a suspicion of a genetic basis for the seizures; however, the patients passed away before genetic evaluations could be conducted.

Neonatal seizures primarily manifest transiently as a consequence of acute lesions such as HIE, meningitis, electrolyte imbalances, and interventricular hemorrhage. Given this context, concurrent assessment and treatment of seizures assume paramount importance. Neonatal seizures increase the risk of seizures in older children (2). Therefore, achieving seizure control with the optimal medication and dosage demonstrates a crucial step for the management of seizure complications and long-term neurodevelopmental sequels.

Despite several studies comparing levetiracetam and phenobarbital as the first-line therapy choice for neonatal seizure control, this topic still needs further clarification. With its extensive experience, low cost, and relative effectiveness, phenobarbital continues to be the preferred choice (7). Food and Drug Administration has not approved levetiracetam for seizure control as monotherapy and has only recommended its use as adjuvant therapy in patients older than one month. In contrast, the European Union has suggested its use as monotherapy for patients above 16 years old (23).

In a study by Ghaffar et al., phenobarbital was more efficacious in controlling neonatal seizures than levetiracetam (24). Similarly, Sharpe et al. reported better phenobarbital seizure control than levetiracetam (7). On the other hand, Gowda et al. compared levetiracetam and phenobarbital for neonatal seizure control and reported 86% seizure control with levetiracetam compared to the 62% observed in phenobarbital demonstrating a significantly better seizure control (25). Similar results have been demonstrated by Grinspan et al. (17). In a study by Wagner et al., levetiracetam and phenobarbital were compared as initial therapy for neonatal seizure control, yielding no significant difference (11). Furthermore, in a comprehensive study by Kumar et al. comparing phenobarbital with phenytoin, lorazepam, and levetiracetam for neonatal seizure control, no significant difference

was found (26). In this study, despite higher rates of seizure control with levetiracetam, no significant difference was observed between the two groups regarding seizure control capability. Additionally, the length of hospital stays and time to initiate enteral feeding were not significantly different.

Limitations

Despite being one of the first studies comparing the effectiveness of levetiracetam and phenobarbital as first-line therapeutic options in an Iranian neonatal population, this study has several limitations. Being single-center and comprising a small sample size limits the statistical power of this study. Given the urgent nature of the disease and the absence of proper blinding and adequate equipment in the emergency department, video electroencephalograms were not utilized as diagnostic criteria. Instead, seizure detection and diagnosis relied on trained staff. Although these professionals are highly skilled, this approach may introduce the risk of bias. Undeniably, due to the lack of infrastructure in developing countries, neonatal seizures are de-diagnosed based on trained medical staff detection and their distinction between spell events and neonatal seizures. Notable baseline differences between the two groups suggest a potential inadequacy in our randomization process, which we addressed through covariate adjustment. Additionally, this study did not evaluated long-term consequences, including neurodevelopmental sequels.

In Conclusion

Neonatal seizures are the most common CNS complication in neonates, which can result in neurodevelopment impairments. Thus, selecting the best first-line therapeutic choice with the best effectiveness and negligible side effects is essential. This study showed no significant difference between levetiracetam and phenobarbital for first-line neonatal seizure control. Further and more comprehensive studies with more significant sample sizes and long-term follow-ups can yield more definitive results comparing the superiority or non-inferiority of these two medications.

Acknowledgment

The authors would like to express their appreciation for the efforts and participation of all parties involved in this study, particularly the patients and their families. Comparing Levetiracetam and phenobarbital as first-line treatment for neonatal seizures (LPNS)

Iranian Registry of Clinical Trials (IRCT) Code: IRCT20220410054471N1

Registration Date: 26/07/2023

Authors' Contributions

Nahideh Khosroshahi Contributed to the study design and conceptualization, data acquisition, and interpretation, and critically revised the manuscript; Kamyar Kamrani**:** Contributed to the study design, data acquisition, and interpretation, and critically revised the manuscript, Muhammadhosein Moradi: Contributed to the study conceptualization, contributed to data analysis and interpretation, and drafted and critically revised the manuscript, Parisa Sadeghirad: Contributed to the study conceptualization, contributed to data acquisition, and drafted the manuscript, and Ayda Khabazi Oskouie Contributed to the study design and conceptualization, contributed to data acquisition and interpretation, and drafted and critically revised the manuscript.

All authors gave final approval and agreed to be

accountable for all aspects of the work.

Conflict of Interest

The authors report no financial or non-financial competing interests.

References

1. Han JY, Moon CJ, Youn YA, Sung IK, Lee IG. Efficacy of levetiracetam for neonatal seizures in preterm infants. BMC Pediatr. 2018;18(1):131.
2. Liu BK, Jiang L, Li XJ, Hong SQ, Chen W, Hu Y. Efficacy and safety of levetiracetam in the off-label treatment of neonatal seizures. Int J Neurosci. 2020;130(4):336-42.
3. El-Dib M, Soul JS. The use of phenobarbital and other anti-seizure drugs in newborns. Semin Fetal Neonatal Med. 2017;22(5):321-7.
4. Shellhaas R. Clinical features, evaluation, and diagnosis of neonatal seizures. UptoDate2022.
5. Mollamohammadi M, Amirhoseini ZS, Saadati A, Pirzadeh Z, Hassan Amouzadeh M. Oral Levetiracetam as Add-On Therapy in Refractory Neonatal Seizures. Iran J Child Neurol. 2018;12(4):103-10.
6. Kaushal S, Tamer Z, Opoku F, Forcelli PA. Anticonvulsant drug–induced cell death in the developing white matter of the rodent brain. Epilepsia. 2016;57(5):727-34.
7. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, et al. Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial. Pediatrics. 2020;145(6).
8. Karaoglu P, Hiz S, Işcan B, Polat A, Ayanoğlu M, Duman N, et al. Intravenous levetiracetam for treatment of seizures in term and preterm neonates. J Pediatr Neurosci. 2020;15(1):15-20.
9. Harris ML, Malloy KM, Lawson SN, Rose RS, Buss WF, Mietzsch U. Standardized Treatment of Neonatal Status Epilepticus Improves Outcome. Journal of Child Neurology. 2016;31(14):1546-54.
10. Torrence C. Neonatal seizures: Part II. Recognition, treatment, and prognosis. Neonatal Network: NN. 1985;4(2):21-8.
11. Wagner CB, Kreimer AM, Carrillo NP, Autry E, Schadler A, Cook AM, et al. Levetiracetam Compared to Phenobarbital as a First Line Therapy for Neonatal Seizures: An Unexpected Influence of Benzodiazepines on Seizure Response. J Pediatr Pharmacol Ther. 2021;26(2):144-50.
12. Van Den Broek M, Groenendaal F, Toet M, Van Straaten H, Van Hasselt J, Huitema A, et al. Pharmacokinetics and clinical efficacy of phenobarbital in asphyxiated newborns treated with hypothermia. Clinical pharmacokinetics. 2012;51(10):671-9.
13. Bittigau P, Sifringer M, Genz K, Reith E, Pospischil D, Govindarajalu S, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proceedings of the National Academy of Sciences. 2002;99(23):15089-94.
14. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: a review. The Journal of Pediatric Pharmacology and Therapeutics. 2015;20(2):76-89.
15. Loiacono G, Masci M, Zaccara G, Verrotti A. The treatment of neonatal seizures: focus on Levetiracetam. The Journal of Maternal-Fetal & Neonatal Medicine. 2016;29(1):69-74.
16. Piña-Garza JE, Nordli Jr DR, Rating D, Yang H, Schiemann-Delgado J, Duncan B, et al. Adjunctive levetiracetam in infants and young children with refractory partial-onset

seizures. Epilepsia. 2009;50(5):1141-9.
17. Grinspan ZM, Shellhaas RA, Coryell J, Sullivan JE, Wirrell EC, Mytinger JR, et al. Comparative effectiveness of levetiracetam vs phenobarbital for infantile epilepsy. JAMA Pediatrics. 2018;172(4):352-60.
18. Mbizvo GK, Dixon P, Hutton JL, Marson AG. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. Cochrane Database of Systematic Reviews. 2012(9).
19. Qiao MY, Cui HT, Zhao LZ, Miao JK, Chen QX. Efficacy and Safety of Levetiracetam vs. Phenobarbital for Neonatal Seizures: A Systematic Review and Meta-Analysis. Front Neurol. 2021;12:747745.
20. Mohamad A. Mikati DT. Neonatal Seizures. Nelson Textbook of Pediatrics2019. p. 3111-6.
21. Maitre NL, Smolinsky C, Slaughter JC, Stark AR. Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures. J Perinatol. 2013;33(11):841-6.
22. Bragg. LVSMFHBN. APGAR Score 2023 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK470569/.
23. Shellhaas R. Treatment of neonatal seizures. UptoDate2022.
24. Ghaffar J, Riaz A, Uzair, Virk AO, Bhatti A. Comparative efficacy of intravenous levetiracetam vs phenobarbitone in neonatal seizures. Med Forum Monthly. 2020;31(7):25-8.
25. Gowda VK, Romana A, Shivanna NH, Benakappa N, Benakappa A. Levetiracetam versus Phenobarbitone in Neonatal Seizures — A Randomized Controlled Trial. Indian Pediatr. 2019;56(8):643-6.
26. Kumar J, Meena J, Yadav J, Saini L. Efficacy and Safety of Phenobarbitone as First-Line Treatment for Neonatal Seizure: A Systematic Review and Meta-Analysis. J Trop Pediatr. 2021;67(1).