

Comparing the Efficacy and Safety of Levetiracetam Versus Phenobarbital as the First-Line Drug in the Control of Neonatal Seizures

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Abstract- Phenobarbital has long been recognized as a first-line treatment for neonatal seizures. However, due to its side effects and variable effectiveness, levetiracetam has emerged as a potential alternative in some studies, though consensus on this issue remains elusive. This clinical trial aims to compare the efficacy and safety of levetiracetam as a first-line agent for managing neonatal seizures. The study involved 40 neonates, aged 36 to 44 weeks gestational age, who were admitted to the neonatal intensive care unit for clinical seizures and met the inclusion criteria. Participants were randomly assigned to receive either phenobarbital (20 mg/kg intravenously over 15 minutes) or levetiracetam (50 mg/kg intravenously over 15 minutes). If seizures persisted or recurred a second dose was given. If seizures continued after the second dose, a second anticonvulsant was added to the treatment regimen. Cessation of seizures for 24 hours duration after drug administration is considered as primary outcome measure. The two groups were compared based on seizure termination, number of doses administered, need for additional medications, and side effects. Baseline characteristics were similar between the two groups. After the first dose, seizure termination rates were 95% for the levetiracetam group and 85% for the phenobarbital group ($P=0.333$). Side effects were reported in 20% of neonates receiving phenobarbital (including two cases of bradycardia and irritability) compared to 5% in the levetiracetam group (one case of irritability) ($P=0.196$). There were no statistically significant differences regarding changes in the treatment regimen or the number of anticonvulsant drugs used. In conclusion, the results of this study indicate that levetiracetam is equally effective as phenobarbital in controlling neonatal seizures and may present a preferable option due to its reduced side effect profile.

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Introduction

Seizure is the most significant and common symptom of serious neurological disorders during infancy (1). It is estimated that seizures occur in 0.1-0.5% of neonates and its rate is 1.5-3 cases per 1000 live births in term neonates and 10-130 per 1000 live births in preterm neonates (2). Seizure is usually associated with poor outcomes, and 7-33% of neonates with neonatal seizures die, and 40-60% of survivors suffer from permanent disabilities, such as cerebral palsy, developmental delay, and epilepsy (3-5).

Hypoxic ischemic encephalopathy is the most common cause of neonatal seizures. Seizures primarily occur in the first 24 hours of birth. The gold standard test for diagnosing and classifying seizures in neonates is continuous electroencephalography (cEEG). However, it is not available in many centers (6). Phenobarbital, used as a first-line treatment, can control neonatal seizures in 33-77% of cases (7). Some acute side effects of phenobarbital include hypotension and a decrease in respiratory function. Chronic exposure to phenobarbital may reduce cognitive ability. Animal studies have also

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found that phenobarbital plays a major role in accelerating neuronal apoptosis in the immature brain (8). Levetiracetam has better efficacy and safety as animal studies have reported no neuronal apoptosis for it. Moreover, it might have neuroprotective effects on the developing brain (9). Recent studies suggest that the use of levetiracetam in comparison with phenobarbital in neonatal seizures has terminated the seizures (77% vs. 46%) (10,11). The first-line treatment in neonatal seizures has not been clarified yet. Thus, the present study was conducted to compare the efficacy and safety of levetiracetam and phenobarbital in the control of neonatal seizures.

Materials and Methods

In this clinical trial, 40 neonates with a gestational age of 36 to 44 weeks who were referred to the Neonatal Intensive Care Unit in Besat Hospital in 2021 due to seizures were included in the study. Consecutive sampling was used in this regard. This randomized and controlled trial was conducted at the level III NICU of tertiary-care center for 18 months. Neonates aged 0-28 days with clinical seizures were included in the study. Neonatal seizures were clinically defined as abnormal, stereotyped and paroxysmal dysfunction in the central nervous system (CNS), occurring within the first 28 days after birth in full-term neonates or before 48 weeks of gestational age in preterm neonates (12). The inclusion criteria included neonates with a gestational age of 36 to 44 weeks, birth weight ≥ 2200 g, and the occurrence of neonatal seizures between the first day and the 28th day after birth. Exclusion criteria of the study included receiving anticonvulsants prior the enrolment, seizures due to hypocalcemia, hypoglycemia, hypomagnesemia, and neonates with congenital malformations such as congenital heart defects, neural tube malformations, diaphragmatic hernia, choanal atresia, esophageal atresia, omphalocele, and intestinal obstruction.

Sample size and its calculation method

The minimum sample size in each group was calculated at 20 neonates based on the study by Gowda *et al.*, (13) in which the percentage of seizure termination for 24 hours in the neonates of the levetiracetam and phenobarbital groups was 86% and 62%, respectively, and given the confidence level of 95% and the test power of 80%, and using the following formula:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 [P_1(1 - P_1) + P_2(1 - P_2)]}{(P_1 - P_2)^2}$$

Intervention

Levetiracetam group (intervention): The patients received a dose of 50 mg/kg of levetiracetam by intravenous infusion for 15 minutes. Phenobarbital group (control): The patients received a dose of 20 mg/kg of phenobarbital by intravenous infusion for 15 minutes. If the seizures did not terminate or returned after 15 minutes, the second dose of drugs would be injected into the patients. If the seizure did not terminate or returned after 15 minutes, even after the administration of the second dose of drugs, the second anticonvulsant drug would be used. The primary outcomes measured in the patients included the complete termination of seizures up to the next 24 hours, the number of doses received to terminate seizures, and the need to add a second anticonvulsant drug. The secondary outcomes measured in the patients were side effects of drugs, including irritability, restlessness, drowsiness, hypotension, bradycardia, need for mechanical ventilation, shallow breathing, and mortality. Complete termination of seizures was confirmed by EEC examination by two unrelated neurologists.

Randomization method

To randomly allocate the patients, a random table of numbers using a simple randomization method was used.

Blinding

The form and volume of the injected drugs were the same, and the physicians, parents, and the person recording the results were not aware of the type of allocation of patients to treatment groups. Moreover, the drugs were prepared by one nurse and injected by another nurse who was not aware of the type of drugs.

Data analysis method

The statistically significant level was considered less than 5%. Data were described using descriptive statistics of mean and standard deviation for quantitative variables and ratio and percentage for qualitative variables. Mann-Whitney test was used to compare quantitative variables and the chi-square test was used for qualitative variables. SPSS 20 Software was used for data analysis in the present study

Ethical considerations

The present study was approved by the research ethics committee of Hamedan University of Medical Sciences with the code of ethics of R.UMSHA.REC.1399.681. It was registered in the clinical trial registration center with the code IRCT20160523028008N23. Also, after providing sufficient explanations about the research objectives, informed consent was obtained from the parents of the neonates if they were willing to participate in the study.

Results

In this clinical trial conducted in 2021, 40 neonates hospitalized for seizures were randomly assigned to two groups: one receiving phenobarbital and the other receiving levetiracetam. The results showed no statistically significant differences between the two groups in terms of gender, mean gestational age, mean weight, and age at the initiation of treatment ($P=1.00$).

The Levetiracetam group showed a higher proportion

of seizure control (95%) compared to the Phenobarbital group (85%), although the difference was not statistically significant ($P=0.322$).

The relative risk (RR) of seizure control in the Levetiracetam group compared to the Phenobarbital group was found to be 3.0, indicating higher control, but the confidence interval is wide (26.0-45.34). (Figure 1, Table 2).

Additionally, none of the neonates in the Levetiracetam group required a second drug for seizure control, while 15% of those in the Phenobarbital group did ($P=0.231$), again indicating no significant difference (Table 3).

In terms of side effects, one neonate in the Levetiracetam group experienced irritability. In the Phenobarbital group, two neonates had bradycardia, and two others experienced irritability.

The relative risk of side effects associated with Phenobarbital was found to be four times higher than that of Levetiracetam (RR=4, 95% CI: 0.48-32.72). However, this difference was not statistically significant (Table 4).

Table 1. Comparison of baseline variables in two study groups

Variables	Levetiracetam group	Phenobarbital group	<i>P</i>
Gender			1.00
Male	10(50%)	10(50%)	
Female	10(50%)	10(50%)	
Age at the initiation of treatment, day	11.1±8.6	6.8±6.2	0.112
Gestational age (mean), week	38.1±1.3	37.9±1.2	0.717
Birth weight (mean), gram	3055.5±424.8	2932.5±507.9	0.295

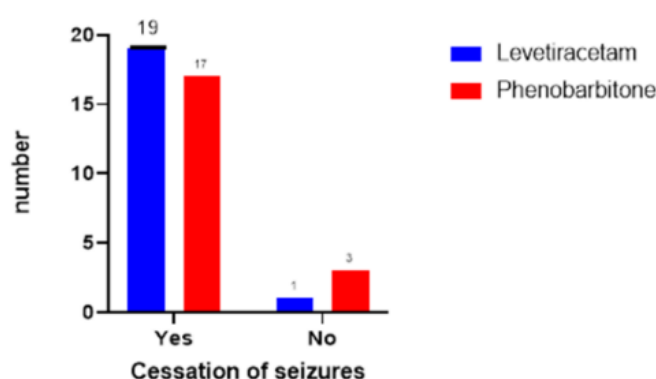


Figure 1. Comparison of seizure cessation after receiving the first dose of the drug

Table 2. Comparison of seizure control after the first dose received in two study groups

Variable	Levetiracetam group	Phenobarbital group	<i>P</i>	RR(95 % CI)
Seizure control				
Yes	19(95%)	17(85%)	0.322	3.0(26.0-45.34)
No	1(5%)	3(15%)		

Table 3. Comparison of the need for the number of doses and receiving the second drug to control seizures in the two study groups

Variables	Levetiracetam group	Phenobarbital group	P
Number of doses			
One	19(95%)	17(85%)	0.605
Two	1(5%)	3(15%)	
Receiving the 2nd drug			
Yes	0(0%)	3(15%)	0.231
No	20(100%)	17(85%)	

Table 4. Comparison of side effects in two study groups

Variable	Levetiracetam group	Phenobarbital group	P	RR(95 % CI)
Side effects				
Yes	1(5%)	4(20%)	0.196	4.0(32.0-72.48)
No	19(95%)	16(80%)		

Discussion

This clinical trial compared the efficacy and safety of levetiracetam and phenobarbital as first-line treatments for neonatal seizures. The findings indicated that both drugs are equally effective, with no superiority of levetiracetam over phenobarbital. However, side effects were four times more common in phenobarbital-treated neonates, though this difference was not statistically significant, likely due to the small sample size. Despite this, phenobarbital remains the first-choice treatment for neonatal seizures because of its effectiveness, although its use is limited by side effects and lack of efficacy in some patients. Previous studies on the efficacy of these two drugs have shown conflicting results. To better understand the obtained results, we will compare them with the findings of previous studies.

Seizure control rates

Our study found that 95% of neonates in the levetiracetam group and 85% in the phenobarbital group achieved seizure control after the first dose, which aligns with findings from another research. For instance, a recent meta-analysis by Qiao *et al.*, (14) reviewed 10 studies involving 930 patients and compared the efficacy of levetiracetam and phenobarbital in controlling neonatal seizures. Results indicated that neither drug was superior, and side effects were fewer in neonates treated with levetiracetam, consistent with our study. Similarly, a meta-analysis by Hooper *et al.*, (15), which reviewed 14 studies involving 1,188 neonates, found that phenobarbital served as a comparison group in three studies. This analysis confirmed that levetiracetam and phenobarbital have similar efficacy in seizure control and

that short-term side effects are fewer with levetiracetam. These findings align with our results.

An observational study conducted by Sharpe *et al.* (16) aimed to evaluate the efficacy and safety of levetiracetam in the treatment of neonatal seizures, 125 neonates were examined, with 66 receiving phenobarbital and 59 receiving levetiracetam. The results revealed that phenobarbital was more effective in treating neonatal seizures; however, it was associated with more side effects.

The study by Gobbur *et al.*, (12) investigated the efficacy of levetiracetam compared to phenobarbital in neonatal seizures. Seventy-eight term and preterm neonates with neonatal seizures hospitalized in the NICU were evaluated. The findings indicated that levetiracetam was effective in 16 patients (41%) and phenobarbital in 19 patients (48.7%). Nonetheless, there was no significant difference between the two groups.

In the interventional study by Akeel *et al.*, (17), the efficacy of levetiracetam and phenobarbital in the treatment of neonatal seizures was compared. The results indicated that seizure control in the levetiracetam group was significantly higher than in the phenobarbital group (78% vs. 65%, $P=0.01$).

Additionally, the study conducted by Bhasin *et al.* (18) demonstrated that phenobarbital is more effective than levetiracetam as a first-line antiepileptic medication in terms of seizure control. However, levetiracetam requires more frequent dosing but exhibits a better safety profile and higher survival rates.

Overall, the results of most studies, with a few exceptions, indicate that levetiracetam is an effective and safe first-line medication for the control of neonatal seizures. The small differences in the results of the studies

can be attributed to the study designs (interventional, prospective, and retrospective), the sample sizes of the patients evaluated, the populations of selected neonates (preterm, term), and the methods used to assess outcomes, particularly clinical versus electrical seizures.

Need for a second dose

In our study, none of the neonates in the levetiracetam group required a second dose, while 15% of those in the phenobarbital group needed additional dosing. This finding aligns with the results from Akeel *et al.*, (17), which reported that seizure cessation occurred after the first dose in 67% of neonates in the levetiracetam group compared to 46% in the phenobarbital group. After one or two doses, 78% of the neonates in the levetiracetam group remained seizure-free for 24 hours, compared to 65% in the phenobarbital group ($P=0.01$). However, this contrasts with the findings of Prasath Ramachandran *et al.*, (19), who observed 36% of neonatal seizures responded to Levetiracetam as first-line antiepileptic drug, 63% of the cases required a second-line antiepileptic drug.

Side effects

One of the primary concerns regarding drug administration is the potential side effects of medications in relation to their efficacy. Studies indicate that, despite its acceptable effectiveness, phenobarbital may be associated with adverse effects such as hypotension, respiratory depression, and apoptosis of nerve cells in preterm neonates, which has led to its limited use. Animal studies have shown that phenobarbital increases apoptotic neurodegeneration and disrupts synaptic maturation in normally developing brains (8,20). In contrast, levetiracetam has been found to reduce apoptosis in damaged brain tissue without affecting synaptic maturation (21,22). A study by Sharpe *et al.*, (16), like our own, demonstrated that the incidence of side effects was higher among neonates receiving phenobarbital compared to those treated with levetiracetam. Specifically, Akeel *et al.*, (17) found no adverse drug reactions in the levetiracetam group, while 23% of neonates in the phenobarbital group experienced adverse drug reactions. Furthermore, other investigations have not reported any serious side effects associated with levetiracetam use in neonatal seizures (23,24). The studies indicated that levetiracetam was associated with fewer adverse effects in neonates, which may enhance its acceptability as a treatment option for seizures in this vulnerable population

Safety and long-term side effects

Although our study focused on short-term side effects, further research is necessary to assess the long-term effects of these medications.

Limitations

First, the statistical power of the study is limited due to its single-center design and small sample size. Additionally, video electroencephalography was not used for diagnosis; rather, the diagnosis relied solely on clinical evaluation. Finally, this study did not evaluate long-term outcomes, including neurodevelopmental effects.

Levetiracetam is an effective and safer alternative to phenobarbital as a first-line treatment for neonatal seizures. However, further investigations may be warranted to confirm these findings and explore their clinical implications

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References

1. Ahmad KA, Desai SJ, Bennett MM, Ahmad SF, Ng YT, Clark RH, et al. Changing antiepileptic drug use for seizures in US neonatal intensive care units from 2005 to 2014. *J Perinatol* 2017;37:3:296-300.
2. Bassan H, Bental Y, Shany E, Berger I, Froom P, Levi L, et al. Neonatal seizures: dilemmas in workup and management. *Pediatr Neurol* 2008;38:6:415-21.
3. Donovan MD, Griffin BT, Kharoshankaya L, Cryan JF, Boylan GB. Pharmacotherapy for neonatal seizures: current knowledge and future perspectives. *Drugs* 2016;76:647-61.
4. Sharma D, Hussain AM, Sharma SS. Efficacy of levetiracetam in neonatal seizures: a systematic review. *J Matern Fetal Neonatal Med* 2022;35:20:3923-30.
5. Uria-Avellanal C, Marlow N, Rennie JM. Outcome following neonatal seizures. *Semin Fetal Neonatal Med* 2013;18:4:224-32.
6. Boylan GB, Stevenson NJ, Vanhatalo S. Monitoring neonatal seizures. *Semin Fetal Neonatal Med* 2013;18:4:202-8.
7. van Rooij LG, Hellström-Westas L, de Vries LS. Treatment of neonatal seizures. *Semin Fetal Neonatal Med* 2013;18:209-15.

8. Bittigau P, Siffringer M, Ikonomidou C. Antiepileptic drugs and apoptosis in the developing brain. *Ann N Y Acad Sci* 2003;993:103-14.
9. Manthey D, Asimiadou S, Stefovsk V, Kaindl AM, Fassbender J, Ikonomidou C, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. *Exp Neurol* 2005;193:497-503.
10. Giva S, Boyle MA, Gorman KM. Should levetiracetam rather than phenobarbitone be the first-line treatment for neonatal seizures? *Arch Dis Child* 2020;105:8:643-6.
11. McHugh DC, Lancaster S, Manganas LN. A systematic review of the efficacy of levetiracetam in neonatal seizures. *Neuropediatrics* 2018;49:12-17.
12. Gobbur RH, Gaduputi G. Efficacy of levetiracetam in neonatal seizures: a prospective open-label comparative study. *Int J Med Pediatr Oncol* 2018;4:1:16-19.
13. 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.
14. 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.
15. Hooper RG, Ramaswamy VV, Wahid RM, Satodia P, Bhulani A. Levetiracetam as the first-line treatment for neonatal seizures: a systematic review and meta-analysis. *Dev Med Child Neurol* 2021;63:11:1283-93.
16. Sharpe C, Reiner GE, Davis SL, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. *Pediatrics* 2020;145:6:e20193182.
17. Akeel NE, Suliman HA, Al-Shokary AH, et al. A comparative study of levetiracetam and phenobarbital for neonatal seizures as a first-line treatment. *Glob Pediatr Health* 2022;9:2333794X221143572.
18. Bhasin D, Sethi A, Chaurasiya OS, Chhabra K. A comparative study on the efficacy and safety of intravenous levetiracetam and phenobarbitone in the treatment of neonatal seizures. *Int J Contemp Pediatr* 2025;12:615-20.
19. Ramachandran HP, Purkayastha J, Lewis LE, Yellanthoor RB, Barche A, Andrade SJ. Levetiracetam as the first-line antiepileptic in neonatal seizures. *Iran J Neonatol* 2020;11:4.
20. Forcelli PA, Janssen MJ, Vicini S, Gale K. Neonatal exposure to antiepileptic drugs disrupts striatal synaptic development. *Ann Neurol* 2012;72:3:363-72.
21. Kılıçdağ H, Dağlıoğlu K, Erdoğan S, et al. The effect of levetiracetam on neuronal apoptosis in neonatal rat model of hypoxic ischemic brain injury. *Early Hum Dev* 2013;89:5:355-60.
22. Komur M, Okuyaz C, Celik Y, et al. Neuroprotective effect of levetiracetam on hypoxic-ischemic brain injury in neonatal rats. *Childs Nerv Syst* 2014;30:6:1001-9.
23. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J. Levetiracetam: safety and efficacy in neonatal seizures. *Eur J Paediatr Neurol* 2011;15:1-7.
24. Sedighi M, Asadi F, Moradian N, Vakiliamini M, Moradian M. Efficacy and safety of levetiracetam in the management of seizures in neonates. *Neurosciences (Riyadh)* 2016;21:3:232-5.