Original article

Comparison of Effect of Phenytoin and Levetiracetam in Neonatal Seizures

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ABSTRACT

Background: Neonatal seizures occur in the first 28 days of life and are a major threat to the neonate's developmental outcome. Phenytoin and levetiracetam are both drugs available as treatment options for neonatal seizures. The objective of this study was to compare the effectiveness of standard recommended doses of phenytoin and levetiracetam in terms of treatment, duration of control, and prevention of recurrence of neonatal seizures at follow-up.

Patients and methods: A randomized controlled trial was conducted in the NICU Department of Central Park Teaching Hospital, Lahore, from 15 February 2022 till 14 February 2023. The study included 80 neonates divided into two groups, Group A and B, having 40 neonates in each. The efficacy of both drugs was compared across these groups. T-test was performed on SPSS and a p-value of less than 0.05 was considered as significant.

Results: There was a significant difference in neonatal seizure control of both the groups of 40 neonates in each group during the hospital stay as well as on 7 days follow up with Levetiracetam being more effective.

Conclusion: Levetiracetam was more effective in comparison with phenytoin in the management of neonatal seizures.

Keywords:

Neonatal seizures, Phenytoin, Levetiracetam

INTRODUCTION

Neonatal seizures are the seizures that occur during the first 28 days of life.[1] The prevalence of seizures in neonatal period is estimated to be 5 per 1000 live births and in preterm neonates is 11 per 1000 live births.[2] Neonatal seizures mostly have subtle manifestations such as ocular changes, tongue thrusting, cycling limb movements, apnea and blood pressure fluctuations.[3] Hypoxic-ischemic encephalopathy (HIE) due to asphyxia, metabolic disturbances, cerebrovascular disease, infection, and congenital malformations are some common causes of neonatal seizures.[4,5] Approximately 7 to 33% of infants die, and 40 to 60% of neonates develop permanent disabilities, which include cerebral palsy, global developmental delay, and epilepsy.[6] Pakistan reports reflect the incidence of neonatal seizures of 4.8% in hospitalized neonates.[7] Phenobarbital, phenytoin, and benzodiazepines are the most common treatment options for neonatal seizures, but there are possible adverse effects of phenytoin and phenobarbital on neuronal tissue and cortical neurons.[8] Levetiracetam has a good efficacy and safety profile as it does not cause neuronal apoptosis or disruption of synaptic development; instead, it may have neuroprotective effects.[9] The efficacy of levetiracetam in controlling neonatal seizures in a study is 86%.[10] Another study shows the efficacy of phenytoin to be 55% in controlling neonatal seizures.[11]

There is limited data at the institutional level about the effect of controlling neonatal seizures with phenytoin and levetiracetam. The objective of this study was to evaluate the effectiveness of levetiracetam compared with phenytoin as a first-line treatment in duration of control and prevention of recurrence of neonatal seizures at follow-up.

PATIENTS AND METHODS

This was a prospective randomized control trial conducted in the Neonatal Department of Central Park Teaching Hospital for a duration of 1 year from 15th February 2022 to 14th February 2023. A total of 80 neonates were included and randomized in 2 groups of 40, each using the opaque envelope technique of randomization. The sample size was calculated from OpenEpi.com based on the number of cases presented in 1 year at our hospital. Neonates with gestational age ≥28 weeks and postnatal age <29 days, birth weight ≥2000 grams and clinical seizures requiring treatment with an antiepileptic medication (according to the diagnosis by the clinician caring for the neonate) were included. Neonates with renal insufficiency, congenital

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anomalies and whose seizures were caused by metabolic, electrolytes disturbances, or hypoglycemia were excluded from the study. After approval from IRB, written informed consent was obtained from the parents of the neonates and a detailed proforma was used by the attending doctor to collect the data from parents and by the clinical assessment of patient after starting medication. Neonates that fulfilled the inclusion criteria were given either of the two drugs, phenytoin (Group A) and levetiracetam (Group B). Seizure control was observed at 24, 48 and 72 hours after drug administration and follow up of 7 days after discharge. All the information regarding their demographics, aetiology of seizures, drug used, gestational age, type of delivery, APGAR score at 1 and 5 minute intervals, seizure subtype, birth weight, intracranial sonography findings, seizure control duration and follow up was documented on the predesigned proforma.

In Group A (treated with phenytoin) loading dose 20 mg/kg with maintenance dose of 5-8mg/kg/24hours twice daily and Group B (treated with levetiracetam) loading dose 20 mg/kg with maintenance dose of 10-60mg/kg/24hours was given twice daily intravenously. Maintenance dose was started after 12 hours of the loading dose and was continued till discharge intravenously and then in oral form on discharge and continued till 7 days on follow-up. If the patient remained seizure free at 7 days follow-up then oral antiepileptic was discontinued. Effectiveness of levetiracetam compared with phenytoin as a first-line treatment, duration of control and prevention of recurrence of neonatal seizures at follow up was accessed.

The mean duration of seizure onset in both groups was first 24 hours of life. Seizures were categorized by the attending doctor on the basis of clinical assessment as there was unavailability of EEG due to limited resources. Seizures were categorized as subtle, tonic, clonic, tonic clonic and myoclonic seizures. Data was entered and analyzed using SPSS version 25.0. T-test was performed to compare the effectiveness of phenytoin and levetiracetam in the treatment of neonatal seizures. A p-value of <0.05 was taken as significant.

RESULTS

There were total of 80 participants, with 40 participants in the Group A (phenytoin) and 40 in Group B (levetiracetam). Their distribution is demonstrated in Table 1.Overall, more male neonates had seizures as compared to females in both the groups with an overall

Table 1: Distribution of participants according to different parameters including gender, gestational age and delivery type

Characteristics	Phenytoin n (%)	Levetiracetam n (%)
Gender		
Male	32 (80%)	29 (72.5%)
Female	8 (20%)	11 (27.5%)
Gestational age		
28 to 36 + 6 weeks	5 (12.5%)	8 (20%)
37 weeks or above	35 (87.5%)	32 (80%)
Delivery type		
SVD	21 (52.5%)	16 (40%)
C-section	19 (47.5%)	24 (60%)

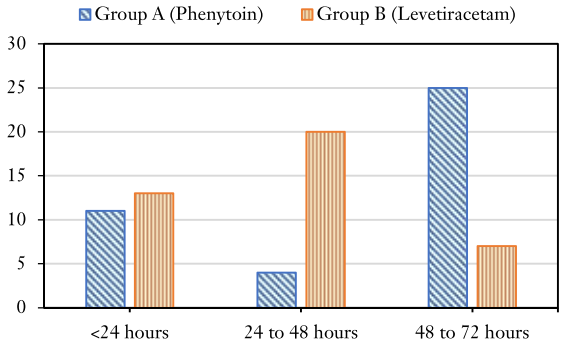

Figure 1: Duration of seizure control between the two groups; phenytoin and levetiracetam.

percentage of 76.25%. Around 83.75% of the participants were of the gestational age 37 weeks or above. SVDs and C-sections, both had a fair share of representation in the data, however more patients had been born via C-section (53.75%).

According to the t-test results, the duration of seizure control was different amongst the two groups. There was significant difference between the two groups, and levetiracetam was more effective, having a quicker duration of seizure control compared to phenytoin (p=0.011) as in levetiracetam group more patients got seizure free within first 24 hours of onset of seizures and likewise seizures control was more in number of patients at 24 to 48 hours and 48 to 72 hours in levetiracetam group. The p-value for follow up at 7 days was also significantly different between both the groups (p-value=0.02) showing greater effectiveness of levetiracetam in preventing recurrence.

This is also demonstrated in Figure 1 above, as Levetiracetam group has more patients in the category of <24 hours owing to quicker duration of seizure control, compared to phenytoin which has a greater number of participants even in the category of 48 to 72 hours.

Other parameters like age, gestational age, delivery type, gender, seizure etiology, intracranial sonography,

Table 2: T-test results of different parameters showing they have no significant difference among both the groups.

Characteristics	Mean		p-value
	Phenytoin	Levetiracetam	
Gender	Male	Male	0.437
Age	1 to 5 days	Newborn	0.13
APGAR at 1 min	4 to 6	4 to 6	1.48
APGAR at 5 min	7 to 10	7 to 10	0.974
Delivery type	SVD	C-section	0.348
Gestational age	37 weeks or above	37 weeks or above	0.994
Seizure etiology	Meningitis	Sepsis	0.193
Seizure subtype	Subtle	Subtle	0.166
Intracranial sonography	Normal	Normal	0.097
Birth weight	2.6 to 3 kg	2.6 to 3 kg	0.432

seizure subtype, APGAR score and birth weight were also studied along with their effect among both the groups. Each parameter was divided into different categories and the most common category was identified. T-tests were also carried out and their results are listed in Table 2 above. The most common category that was present for each parameter in both the groups has also been added under the Mean.

Most common seizure subtype was subtle seizures with a prevalence of 98.75%, whereas 1.25% seizures were tonic. Most common cause of seizures overall was hypoxic ischemic encephalopathy (HIE) as there was history of birth asphyxia in these patients with 30 (37.5%) participants having it whereas other causes included meningitis (27.5%), sepsis (25%) and in 10% of the participants' cause could not be identified. Out of these, meningitis was the most common cause among Group A participants whereas sepsis was the most common cause among Group B participants.

DISCUSSION

Seizures remain a serious dilemma occurring during the neonatal period and are more common in low birth weight and preterm neonates with significant associated morbidity and mortality.[12] Even though there are many advances in medical research and patient care, the frequency of neonatal seizures remains 1.5 to 3 in 1000 live births along with a 20% mortality rate.[13] Neonatal seizure may be classified into four types; subtle, tonic, clonic and myoclonic seizures, out of which subtle seizures are the most common type.[14] This was also observed in this study. Neonatal seizures occur due to different underlying cerebral pathologies including hypoxic ischemic encephalopathy which is one of the most common causes.[14,15] Other causes include ischemic stroke, epilepsy, infections of the central nervous system including meningitis, sepsis and intracranial hemorrhage.[14] Neonates are more susceptible to seizures as their neurons are still immature and any minute changes in neurotransmitter levels have a profound effect on them.[13] Convulsions when occur in a neonate or an infant are an emergency and require urgent diagnosis and treatment, not only to control the acute attack but also minimize any possible damage to the brain and central nervous system.[14] For this purpose, many anti-epileptic drugs have been used, out of which Phenobarbital is given as the first-line treatment.[12,14] Phenytoin and levetiracetam are usually given as second-line drugs, especially in nonresponding cases.[12,16,17.] in our area as injectable phenobarbital availability is very difficult due to drug shortage in many areas of Lahore so this drug was not used moreover there are limited studies present on comparison of levetiracetam and phenytoin especially in neonatal seizures so our main focus was to compare these to easily available drugs. Phenytoin acts on voltage-dependent sodium channels whereas levetiracetam decreases presynaptic neurotransmitter release.[14,18.] Other drugs used to treat neonatal seizures include benzodiazepines and lidocaine.[14] Levetiracetam has also been used as a monotherapy and also given in different seizure types as it has a broad spectrum of antiepileptic activity.[17,19,20] It has non-hepatic elimination and binds less to proteins and also has lesser adverse effects because of which it is considered a safer drug compared to phenytoin.[21]

It has been noted in a study that neonates with hypoxic-ischemic encephalopathy responded best to phenobarbital whereas those with congenital heart diseases responded better to levetiracetam.[22] However, current data suggests that levetiracetam and phenytoin both are used as second line drugs in the treatment of neonatal seizures. Even though levetiracetam is safer, there is not enough data to prove it is more efficacious.[23,24] One previous study in 2023 suggested that there is no significant difference in the efficacy of levetiracetam and phenytoin.[12] Another study also reported that levetiracetam is good as a second-line drug and is safer, however there is no evidence that it is superior to phenytoin in terms of efficacy.[25]

another study shows that levetiracetam controls clinical seizures more effectively without EEG monitoring (71%–93%).[26] In a randomized controlled trial of 100 neonates presenting with clinical seizures, seizures were stopped in 86% of those randomized to levetiracetam and 62% to phenobarbital ($p<0.01$) showing greater efficacy of levetiracetam.[27]

Results add these data and prove that phenytoin and levetiracetam both effectively treat neonatal seizures. Levetiracetam, however seems to have a

greater efficacy and quicker duration of seizure control compared to phenytoin. More research is required on a larger scale with a greater sample size to further build on this finding.

This study was conducted in only one hospital. Studies from other hospitals across the country are needed to generalize the findings. The serum levels of both drugs were not checked in the patients as it was expensive and unavailable in local setting. Moreover, the adverse effects of both drugs were not checked in patients.

CONCLUSION

Levetiracetam has shown more effectiveness, but the drug's safety could not be evaluated. Phenytoin and levetiracetam may be considered effective alternative drugs in the treatment of neonatal seizures, though levetiracetam seems to be more effective. It could be the first choice drug in treating neonatal seizures, but more studies may be required with a larger sample size to determine its effectiveness.

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