ORIGINAL ARTICLE

Comparing the Efficacy and Safety of Levetiracetam Versus Phenytoin for Treating the Acute Phase of Neonatal Seizures

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Abstract

Objectives

Neonatal seizure is a significant problem in this life course, and its timely and effective treatment is crucial. In this study, we compared the efficacy of levetiracetam versus phenytoin for treating the acute phase of neonatal seizures.

Materials & Methods

In this single-blind case-control study, 60 consecutive children with neonatal seizures referred to the Children's medical center in Tehran, Iran, in 2018 were studied. Those neonates who had at least 30 minutes of seizure after Phenobarbital treatment were assigned to receive either phenytoin (20 mg/kg) or levetiracetam (initial dose of 40-60 mg/kg) through block randomization. The efficacy and safety of the two drugs were compared between the groups.

Results

The response rate was 83.3% and 86.7% in phenytoin and Levetiracetam groups, respectively, which was not significantly different between groups (P=1.000). Adverse effects were nearly similar between groups (6.7% in the phenytoin group and 3.3% in the Levetiracetam group, P=1.000).

Conclusion

Levetiracetam and phenytoin are both practical and safe for treating neonatal seizures.

Keywords: Neonatal Seizures; levetiracetam; phenytoin; safety; efficacy
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Introduction

Neonatal seizure is a significant problem due to various factors, such as benign familial or life-threatening cases with central nervous system anomalies (1). A seizure is usually the first neurological symptom and may affect the long-term prognosis (1). The seizure may demonstrate a curable etiology and prompt diagnosis and treatment of the underlying etiological factors resulting in improved outcomes (1). Correspondingly, the seizure may require some urgent approaches to reduce the probable cerebral injuries (1, 2). In some cases, neonatal seizures are accompanied by early mortality or delayed neurological impairments that may affect the developmental course and cause post-neonatal epilepsies (2). The prevalence rate of neonatal seizures ranges from 1.8 to 8.6 per 1000 live births, and these differed reported rates may be due to some diagnostic challenges or various applied definitions for seizure (3-5). A definite diagnosis of seizure is usually challenging (6). Substantially, the seizures are seen in the first week of the neonatal period (7). The seizure incidence rate ranges from 1.5 to 5.5 cases per 1000 neonates (8-10). Low gestational age and birth weight are related to increased disease severity (11, 12). Phenytoin is a first-line option for treating neonatal seizures (13, 14). Furthermore, levetiracetam is a good option among the second-line medications, especially in stable chronic cases *older than four years (15-18).* However, in some reports, it has shown promising efficacy in the acute phase of neonatal seizures (19) , whilethe definite efficacy of this drug is not yet understood. Hence, in this study, we *investigated* the safety and efficacy of *levetiracetam compared to phenytoin for treating the acute phase of neonatal seizures.*

Materials & Methods

In this single-blind randomized clinical trial, 60 consecutive children with neonatal seizures who were referred to Children's Medical Center, Tehran, Iran, in 2018 were enrolled. The inclusion criteria were gestational age of more than 37 weeks, birth weight over 2500 grams, postpartum age under 28 days, seizures due to Hypoxic-Ischemic Encephalopathy (HIE) according to electroencephalography (EEG), focal or multi-focal seizures, intracranial hemorrhage (ICH), central nervous system infections, genetic syndromes, focal or extensive malformations, idiopathic or genetic seizures, metabolic disorders other than electrolyte problems or renal failure, receiving Phenobarbital 20 mg/kg, lack of response to initial anti-convulsants, and parents assigned informed consent.

Preterm neonates, cases with dissatisfied parents, drug intolerance or hypersensitivity, serum creatinine more than 1.2 on admission or more than 2 mg/dl at any other time, biochemical disorders such as hypoglycemia, hypocalcemia or electrolyte imbalance, and severe life-threatening hypoxic-ischemic injuries were excluded from the study. This study was performed under the principles of the Declaration of Helsinki and approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS) (Ethical code#: IR.TUMS.CHMC.REC.1397.034).

Neonates with seizures prolonged at least 30 minutes after Phenobarbital treatment were assigned into two groups of receiving either phenytoin (20 mg/kg) or levetiracetam (initial dose of 40-60 mg/kg) using block randomization. Randomization was done by Excel version 2016 (Microsoft, USA). Patients were blind about the type of drug. Clinical and laboratory findings besides EEG alterations

were recorded and compared between the two groups. The adverse effects were compared by laboratory assessment in the first 48 hours. Besides, the vital signs were monitored. In responsive cases, the phenytoin maintenance dose was 5 mg/kg/day twice a day every 12 hours, and the levetiracetam maintenance dose was 40-60 mg/kg/day in two separate doses.

Statistical Analysis

Data analysis was done using SPSS statistical software (version 23.0 for Windows; IBM SPSS Statistics, Armonk, NY, USA). The results were expressed as mean and standard deviation (mean ± SD) for the quantitative variables and percentages for the qualitative variables. The frequency was calculated for qualitative variables, and the mean and standard deviation were calculated for quantitative variables. *The utilized tests to comparevariables between groups were Chi-Square for* qualitative variables*, Independent-Sample-T for* quantitative variables*, and Fisher's tests for categorical variables. The P-values under 0.05 were considered statistically significant.*

Results

The mean age was 9.43 and 9.5 days in the phenytoin and levetiracetam groups, respectively (P=0.969). 40% of the phenytoin group and 50% of the levetiracetam group were males (P=0.436). The delivery method was the cesarean section in 76.7% and 73.3% of phenytoin and Levetiracetam groups, respectively (P=0.766). The mean birth weight (P=0.836) and gestational age (P=0.797) were similar between the two groups (Figures 1 and 2). and also efficacy and safety of phenytoin and levetiracetam are comparable (Figure 3).

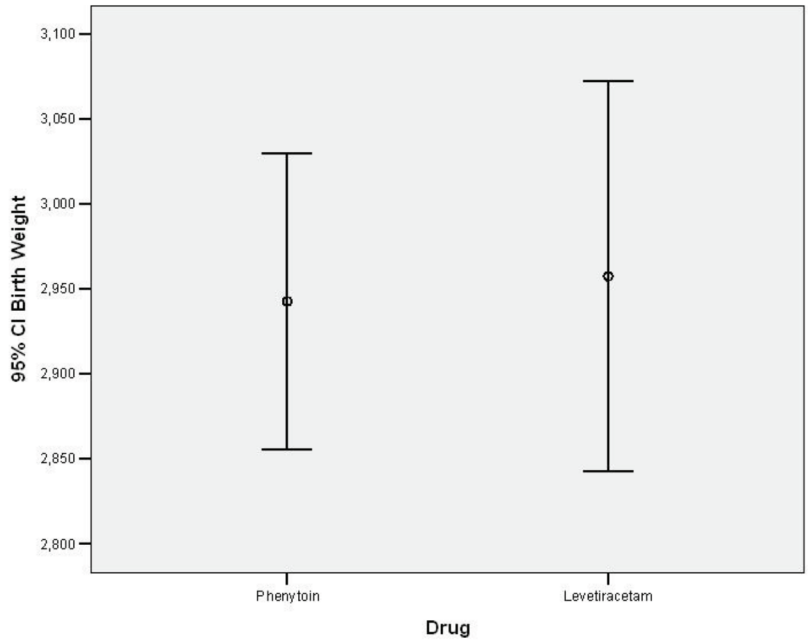

Figure 1*. Birth weight across the groups*

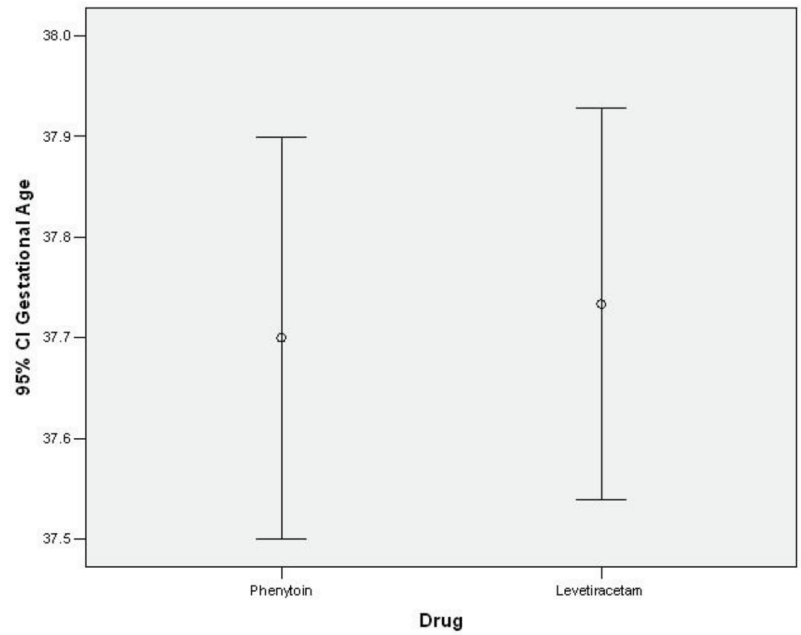

Figure 2. *Gestational age across the groups*

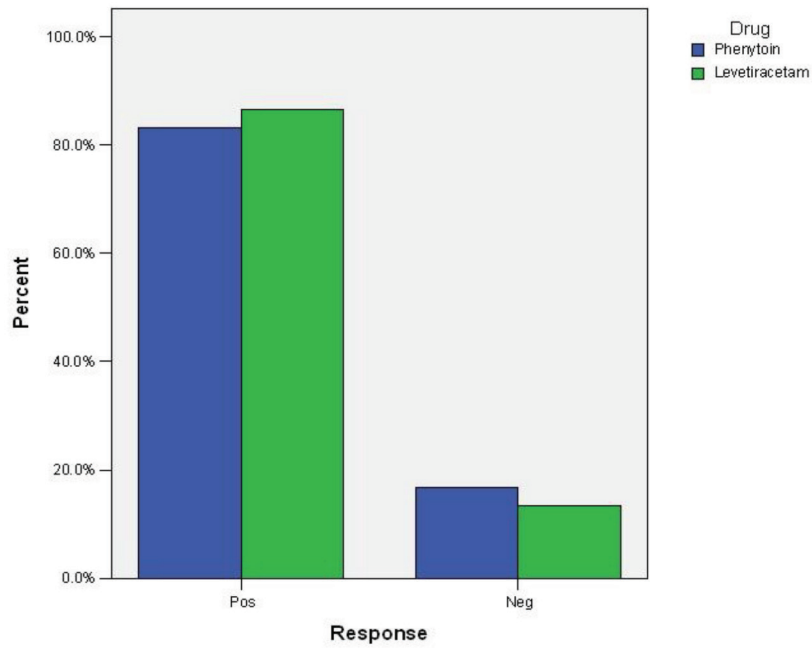

Figure 3. *Therapeutic outcomes across the groups The response rate in the phenytoin group was 83.3%, and in the Levetiracetam group was 86.7%, which was not significantly different between groups (P=1.000) (Figure 3). The adverse effects were almost similar in both groups that were seen in 6.7% and 3.3% in phenytoin and Levetiracetam groups, respectively (P=1.000).*

Discussion

Seizure is a life-threatening problem during the neonatal period with a raised incidence and mortality rate in preterm and low birth weight neonates. It is usually treated with Phenobarbital as the first-line treatment. However, in non-responding cases, other medications, such as phenytoin and levetiracetam, are recommended (20). Levetiracetam is an intravenous medication initially introduced in 2006; it could be used in

cases without phenytoin access or those leading to adverse effects , and reportedly, it is effective intreating resistant patients (21,22). The efficacy and safety of phenytoin and levetiracetam are compared in the current study.

Wu et al. (23) showed a significant reduction in partial-onset resistant seizures in patients treated with levetiracetam compared to placebo; the treatment was accompanied by mild to moderate adverse effects similar to the present study. Abend et al. (24) reported a 35 percent efficacy for levetiracetam, which is consistent with this study. However, Ramantani et al. (25) assessed the efficacy and safety of levetiracetam in cases with neonatal seizures and demonstrated that two-thirds of cases had a good response for four weeks, and no adverse effects were found.

Levetiracetam has been effective in cases resistant to monotherapy (26). Venkatesan et al. (27) showed that levetiracetam is effective in treating cases with neonatal seizures of HIE origin. Shin et al. (28) demonstrated that levetiracetam was effective in 94 percent of cases with neonatal seizures with no significant adverse effects. The current research also found that levetiracetam has remarkable efficacy, and its side effects are mostly mild.

Mollmohammadi et al. (29) showed that more than 95 percent of cases with seizures could be treated with oral levetiracetam, which is helpful in cases without access to intravenous preparation. It has shown promising efficacy and safety in preterm cases (30). In the present study, all neonates were low-risk, including term and normal birth weight cases. The efficacy and safety of levetiracetam and phenytoin were similar. Furthermore, the other possible confounding factors were similar between the groups.

In Conclusion

according to the results, levetiracetam and phenytoin are both effective and safe for treating neonatal seizures. However, further studies with larger sample sizes and multi-center samplings are required to attain definite results in this era.

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Author's Contribution

Study concept and design:' Mahmoud Mohammadi, Kadivar Maliheh'. Collection of data. Adhami Pegah .Analysis and interpretation of data: Mirnia Kayvan'.Drafting of the manuscript: ' Sangsari Razieh '.Critical revision of the manuscript for important intellectual content: 'saeedi maryam'.

Conflict of Interest

The authors declared no conflict of interest.

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