

Efficacy of Phenobarbital, Italept, and Topamax in the Treatment of Neonatal Seizures: A Double-Blinded Cross-Sectional Study of the Iranian Population

Shahram Sadeghvand^{1,2}; Leila Islamian Ghadim³; Mir Hadi Mousavi ¹; Gisou Erabi ⁴

¹ Pediatric Health Researches Center, Department of Pediatrics, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

² Department of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran

³ Clinical Research Development Unit of Children Hospital Tabriz University of Medical Sciences, Tabriz, Iran

⁴ Student research committee, Urmia university of medical sciences, Urmia, Iran

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ABSTRACT

Objectives

Seizures are changes in the electrical activity of the brain. These changes can cause significant or otherwise asymptomatic symptoms. Phenobarbital and phenytoin are known drugs for treating neonatal seizures, but little clinical experience exists using other drugs. The present study aims to evaluate the efficacy of other drugs, such as Levetiracetam and Topiramate, compared to Phenobarbital in treating neonatal seizures.

Materials & Methods

In a double-blind clinical trial, all neonates admitted to a referral hospital for two years (2020-2022) due to seizures were included. All of the neonates were treated with a dosage of 10-40mg/kg/state IV Phenobarbital to control the acute seizure. After that, they were divided into three groups with specific treatment programs. Groups were ordered with oral Phenobarbital 5mg/kg/day maintenance (first group), oral Topiramate 3-8mg/kg/day (second group), and 10-40mg/kg/day Levetiracetam (third group). Seizures and potential side effects were investigated through interviews and medical EEG tests. The data was analyzed using the Chi-square test.

Results

Sixty infants (20 neonates in each group) were studied. Phenobarbital, Italept, and Topiramate did not significantly differ in controlling convulsions and changes related to brain paroxysmal discharges.

Conclusion

Due to the long treatment duration and side effects, it is essential to choose the appropriate drug for treating treatment-resistant seizures of neonates. The present study found that Phenobarbital, Levetiracetam, and Topiramate are equally effective in controlling seizures. These medications can also help eliminate abnormalities in children's brain paroxysmal.

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***Corresponding Authors:** Mousavi MH, MD. Department of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran. Email: mirhadimousavi33@yahoo.com; Erabi G, MD. Student Research Committee, Tabriz University of Medical Sciences, Golgasht Street, Tabriz. Email: gisou.erabi@gmail.com



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Introduction

A seizure is a transient physiological disorder of the brain caused by abnormal electrical discharges of a group of cortical neurons whose shape depends on the function and replacement of these neurons (1). It is defined as a temporary occurrence of signs and/or symptoms resulting from abnormal synchrony or excessive brain neuronal activity. Seizures are the most common neurological emergency in newborns, occurring in 1 to 5 every 1000 live births (2). The immature brain of the neonate is more susceptible to developing seizures. In addition, different types of seizures occur in neonates.

Seizures cause fear and anxiety in the patient and their family. In this regard, eliminating the cause of seizures is a fundamental challenge for physicians and patients. The most common causes in neonates include hypoxic insult at birth, electrolyte disturbances, hemorrhage or stroke, infection, structural disorders of the brain, drug withdrawal, and epilepsy syndromes (3).

Seizures are often overlooked because they are challenging to recognize clinically. Unlike older children and adults, neonates do not always show obvious clinical symptoms during seizures. Like other patients with critical disease, most neonatal seizures are subclinical—they do not have obvious clinical symptoms and are, in most cases, diagnosed by electroencephalography (EEG)(4, 5).

Various medications are used to control seizures. The drug is used based on the type of attack and its effectiveness and safety. If the correct medication is prescribed and used correctly, seizures can be controlled in 70% to 80% of patients.

According to international guidelines, Phenobarbital is the most commonly recommended agent for the first-line treatment of

neonatal seizures. After administering a single-loading dose of Phenobarbital, most seizures are controlled (6).

If standard medications fail to control seizures after repeated doses, doctors may consider using infusions. Maintenance anticonvulsants should be started in newborns with EEG-confirmed seizures. In neonates with a clinical event without EEG evidence of seizures, the maintenance dose can be discontinued, and the EEG can be checked frequently to prevent the neonate from having an EEG seizure later. With the approval of new-generation anticonvulsant drugs and considering that a second drug is needed for seizure control in some neonatal seizures, it was necessary to compare the effect of new anticonvulsant drugs and detect the possible side effects of these drugs. Phenobarbital, Topiramate, and Levetiracetam are taken orally to control neonatal seizures. A recent investigation into the potential side effects of these drugs found no significant differences in their effectiveness at controlling seizures and brain waves in newborns.

Materials & Methods

Study design, treatment regimen, and ethics approval

The study's statistical population was all neonates who, in the last two years from 2020 to 2022, have been referred to Tabriz Children's Hospital, Iran, due to seizures and have been treated with Phenobarbital, Italept, and Topiramate to control seizures. Patients were divided into three groups; for 20 of them, Phenobarbital 20 Italept (made in Italy) and 20 Topiramate (made in the United States) were administered. These individuals were matched with participating in the study regarding demographic characteristics. There were four types of seizures in neonates: Automatism (39%),

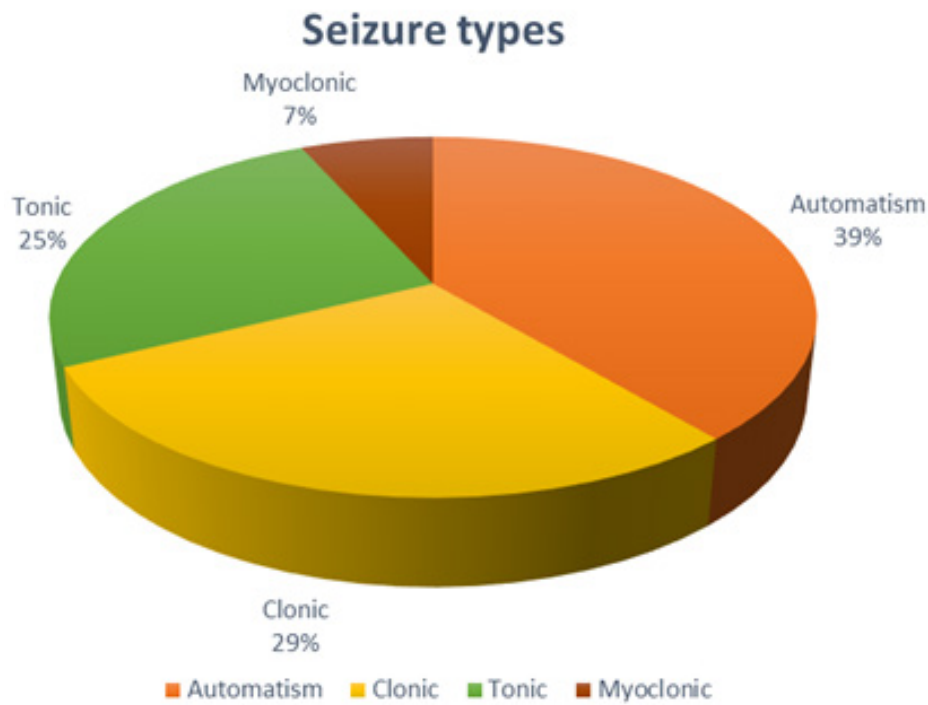


Figure 1. As it is shown in the chart, all types of seizures in neonates were divided into 4 categories: (1) Automatism (39%), (2) Clonic (29%), (3) Tonic (25%), and (4) Myoclonic (7%)

Clonic (29%), Tonic (25%), and Myoclonic (7%) (75%), HIE (Hypoxic-Ischemic Encephalopathy) (21%), and Metabolic disorders and Brain hemorrhage (4%) (Figure 2). In this study, seizure occurrence in neonates was due to three causes: Idiopathic

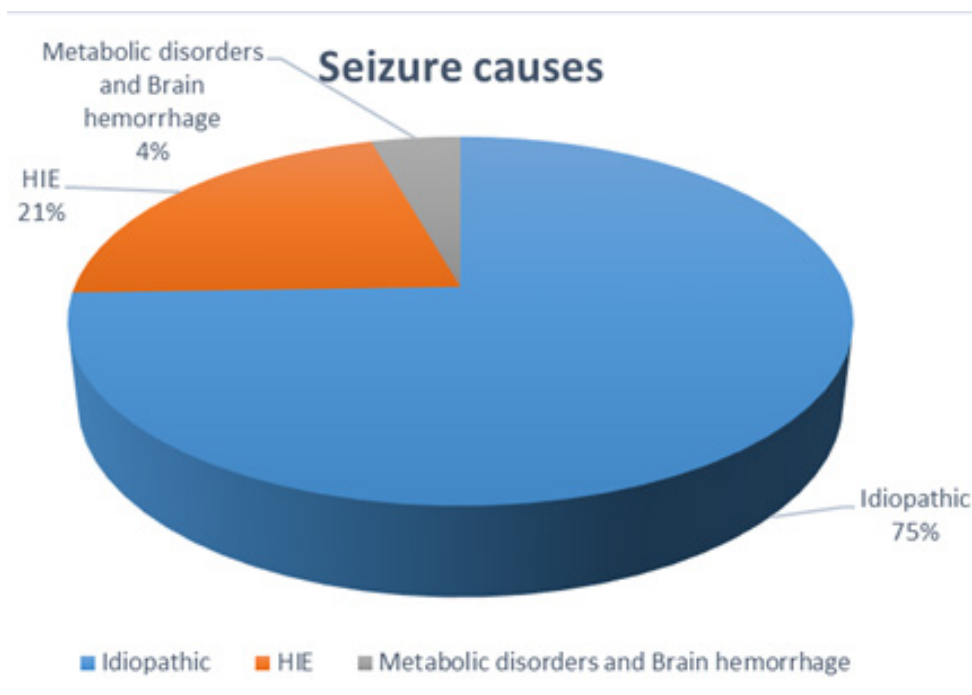


Figure 2. As it is shown in the chart, in our study there were 3 causes of seizure occurrence in neonates: (1) Idiopathic (75%), (2) HIE (Hypoxic-Ischemic Encephalopathy) (21%), and Metabolic disorders and Brain hemorrhage (4%)

The current research was approved and registered in the Research Council of Tabriz Medical School with the ethical code IR.TBZMED.REC.1398.1077 and also with IRCT 20200115046137N1 code.

In the first stage, for all neonates administered to the emergency room with the diagnosis of the neonatal seizure (confirmed by a neurologist in the pediatric field), primary ABCDE assessment and resuscitation were checked. After that, a reliable IV line was imitated. Furthermore, after the diagnosis of acute seizure, IV Phenobarbital with a dosage of 10-40mg/kg/state was given to control the acute seizure (as indicated in the Guidelines). According to national and international protocols, Phenobarbital is a routine drug in the control of acute seizures, and all centers at different levels have access to 200 mg Phenobarbital ampoules, and all general practitioners are familiar with this

drug. Besides, in our level 3 treatment center, there are both oral and intravenous types of these drugs in the emergency room, NICU, and neonatal department. After the initial control of acute neonatal seizure, all neonates were divided into three groups, and a specific treatment program was administered for each one. These three groups of children with seizures confirmed by a neonatologist and pediatric neurologist were randomly selected by computer randomization. For the first group, the intervention based on the oral Phenobarbital (made in Iran) 5 mg/kg/day maintenance dose was done, and for the second group, the intervention based on the oral Italept 10-40 mg/kg/day and for the third group oral Topamlex 3-8 mg/kg/day were done (Figure 3). All neonates continued treatment for three months, and they were monitored for six months for recurrent seizures or side effects. After two

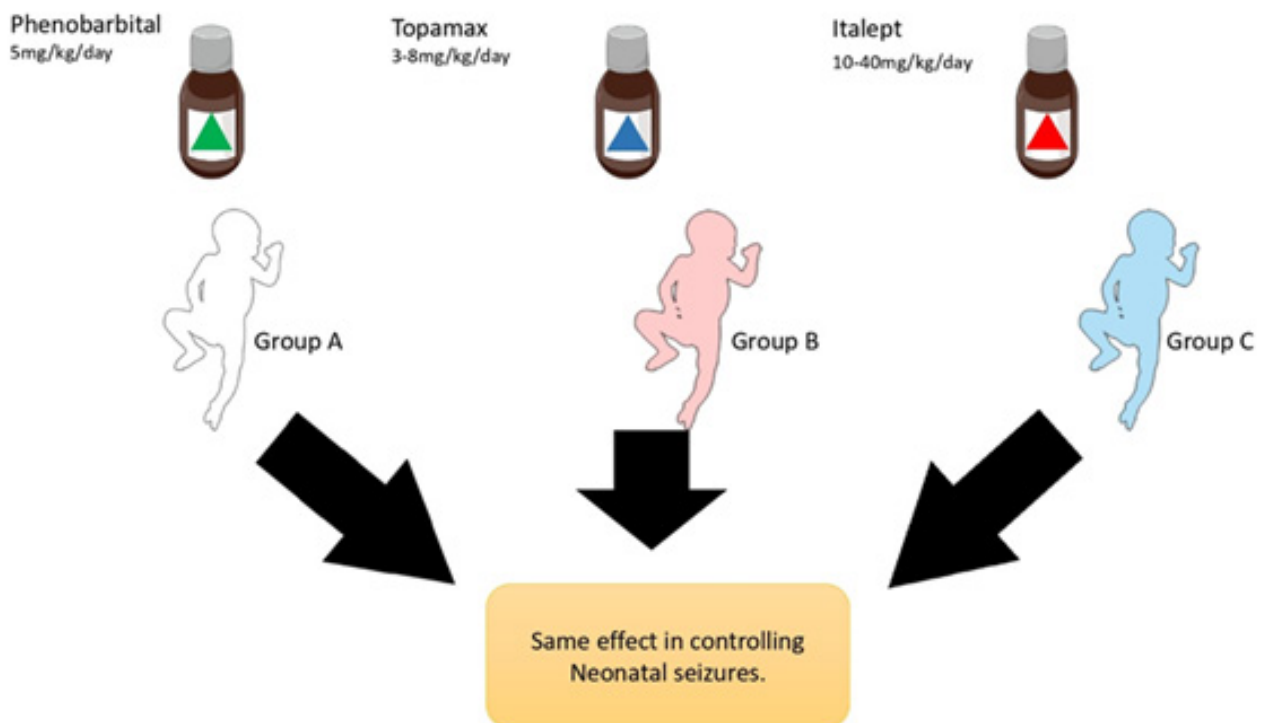


Figure 3. After the initial control of acute neonatal seizure with oral Phenobarbital 10-40 mg/kg/state, all neonates were divided into three groups, and a special treatment program was administered for each one. For the first group an intervention based on oral Phenobarbital 5mg/kg/day maintenance dose, for the other group an intervention based on oral Topiramate 3-8mg/kg/day and for the third group an intervention based on 10-40mg/kg/day Levetiracetam was done

weeks of treatment initiation, two patients who received Phenobarbital experienced nausea and vomiting, so their drug was changed to Italept. No significant side effect was observed when administrating Italept or Topamax. Phenobarbital administration can cause some other side effects, such as depression in the respiratory, hypotension, and neural apoptosis in neonate brains that have not been mature enough (7, 8), but none of these adverse effects were observed in the studied patients. During hospitalization, the neonates were examined by neonatologists and neurologists for seizures and possible side effects through interviews with parents and medical EEG tests to determine which drugs had the most significant impact on the child’s seizures and all neonates included in this study were followed for six months after the occurrence of first seizure — in hospital and at home (after being discharged) —and controlled if the seizure happened again. All infants received anticonvulsant therapy, and no infants were excluded from treatment in this study.

Statistical analysis

The present study is a double-blind clinical

trial and preparing a questionnaire containing demographic information and information about the type of seizure, the underlying cause, severity, duration of seizures, recurrence of seizures and frequency of attacks and type of seizures, and symptoms of possible complications accompanied by parents of children. Drug side effects in each group were arranged and compared in Tables. The data were analyzed using SPSS version 23 with descriptive statistics and Chi-square analysis.

Results

The gender distribution of the participants was the same in this study. Thirty neonates (50%) were male, and 30 (50%) were female. Because a wide range of drug complications can happen in preterm neonates and the metabolism of the drugs used for treatment can be different, all of the neonates included in this study were GA>36 weeks.

This section (Table 1) uses descriptive statistics and a Chi-square statistical index to analyze the data.

Table 2 shows no significant difference between the two groups of Topiramate and Phenobarbital (F = 3.52, p = 0.52).

As shown in Table 3, no significant difference

Table 1. Time of seizure (according to the neonates’ age)

	First day	First week	Week 1-2	After 2 weeks
Number of neonates	4 cases	24 cases	12 cases	20 cases

Table 2. Chi-square test results to compare the two groups of Topiramate and Phenobarbital drugs

	value	fd	Sig.
Chi-square Test	0.52	1	3.52

Table 3. Chi-square test results to compare the two groups regarding the difference between Topiramate and Levetiracetam

Chi-square Test	value	fd	Sig.
	0.43	1	4.04

($F = 4.04$, $p = 0.43$) was found between the two groups of Topiramate and Levetiracetam.

Table 4 shows no significant difference between the two groups due to Phenobarbital and Italept ($F = 4.81$, $p = 0.31$).

All neonates with seizures were tested with EEG two times: first initially to hospitalization and second a week after controlling seizure. During the follow-up, the results of EEG testing were as important as parents' answers.

Table 5 indicates no significant difference in EEG between the two groups due to Phenobarbital and Topiramate ($F=5.07$, $p=0.47$).

Table 6 depicts no significant difference in EEG between the two groups due to Phenobarbital and Levetiracetam ($F=5.19$, $p=0.82$).

Table 7 illustrates no significant difference was found in EEG between the two groups due to Phenobarbital and Levetiracetam ($F=5.19$, $p=0.82$).

Table 4. Chi-square test results to compare the differences between the two groups regarding the Phenobarbital and Italept effects

Chi-square Test	value	fd	Sig.
	0.31	1	4.81

Table 5. Chi-square test results to compare the two groups regarding the difference of the EEG tests between Phenobarbital and Topiramate

Chi-square Test	value	fd	Sig.
	5.07	1	0.47

Table 6. Chi-square test results to compare the two groups regarding the difference of the EEG tests between Phenobarbital and Levetiracetam

Chi-square Test	value	fd	Sig.
	5.19	1	0.82

Table 7. Chi-square test results to compare the two groups regarding the difference of the EEG tests between Levetiracetam and Topiramate

Chi-square Test	value	fd	Sig.
	5.55	1	0.58

Discussion

Phenobarbital is one of the oldest, least complicated, and cheapest drugs used to treat seizure disorders. The drug is approved by the World Health Organization as the first line of treatment for neonatal seizures in developing countries (9-11). While Phenobarbital is an option for managing seizures in children, its use is controversial because of reported behavioral side effects. In developed countries, its use has declined in favor of newer medications that have less impact on behavior. However, Phenobarbital remains a first-line treatment in situations where other drugs are banned due to severe blood or liver issues or when cost is a significant concern (12).

Italacet is a Piracetam-derived drug approved by the FDA in March 2007 as extra and adjunctive therapy for primary generalized Tonic-Clonic seizures in children. Other studies are effective in myoclonic in resistant adolescents and patients with partial refractory seizures. Furthermore, this drug has fewer clinical side effects and interactions than first-line drugs (13).

Italept exhibits rapid and thorough digestive absorption; however, it demonstrates a low rate of protein binding. The drug undergoes partial metabolism through enzymatic hydrolysis and operates independently of the cytochrome system. Both the drug and its metabolites are eliminated via urine, with a half-life ranging from approximately 6 to 8 hours. It does not disrupt the occurrence of other epileptic seizures and does not influence the pharmacokinetics of other medications, including contraceptives, digoxin, and warfarin. This drug is an adjunct in controlling partial and generalized epilepsy(3).

The present study's results showed no difference between Topiramate, Phenobarbital, and Italept in

treating neonatal seizures. The study of Nemati et al. showed that keppra (Levetiracetam) is more cost-effective than Phenobarbital and can be used as a quality drug and as an alternative to Phenobarbital (14). Evidence suggests that factors related to demographic characteristics, drugs, seizure-related factors, and physiological variables affect the quality of life of children (15, 16). To improve the community's health and consequently increase the quality of life in patients, policymakers should seek appropriate solutions to identify factors that reduce or increase the quality of life in children and improve the community's quality of life and health. Throughout the study, the effectiveness of Phenobarbital and Levetiracetam was the same. Still, due to fewer drug interactions, fewer side effects, a lack of need for routine tests, and blood levels of the drug in Italept, it can be suggested as an effective treatment for neonatal seizures. Notably, Levetiracetam , as a new-generation drug, requires long-term cohort studies for efficacy and long-term side effects. In Lekha's study, conducted in 2018 to compare the effectiveness of Levetiracetam with Phenobarbital in neonates with hypoxic brain injury, Levetiracetam was suggested as an excellent alternative treatment to Phenobarbital. Another study by Zakary et al. aimed to compare Levetiracetam's efficacy with Phenobarbital in infantile seizures in 2018, indicating that Levetiracetam was more effective (17).

Intravenous Phenobarbital and phenytoin are the first line of treatment for these patients and are used in most medical centers(18).

Midazolam infusion is one of the proper therapeutic methods to control the disease in treating persistent epilepsy and cases of failure of first-line drugs (19). Midazolam is a water-soluble

benzodiazepine, allowing for faster neurological evaluation of the condition after an attack. This drug is the only anticonvulsant drug that can be administered intramuscularly or intranasally by mouth. Its therapeutic efficacy by intranasal is 79% and 82 to 100% nationally.

Failure to treat with Phenobarbital and phenytoin refers to attacks that continue due to the adequate blood levels of these drugs (20). Because the pharmacokinetics of anticonvulsant medications and their required doses in different age groups are affected by physiological changes(21), it will not be possible to judge the failure of Phenobarbital and Phenytoin drugs and the usefulness of Midazolam infusion in treating these patients without determining the blood level of these drugs.

Levetiracetam is a Piracetam-derived drug approved by the FDA in March 2007 as adjunctive and extra therapy for primary generalized Tonic-Clonic seizures in adults and children over six years of age and in other studies on juvenile myoclonic attacks. It is also effective in patients with refractory partial epilepsy and has fewer clinical side effects and drug interactions than other first-line drugs (19).

In this study, Topiramate was not different from Italept in controlling neonatal seizures. Due to the side effects of Topiramate, specifically in long-term use in the form of glaucoma, acidosis, hyperthermia, and sometimes kidney stones and cognitive disorders in older age, this drug cannot be considered the first line in the treatment of neonatal seizures. However, no complication in this study may have been due to short-term follow-up. Moreover, Phenobarbital has side effects such as sedation, and in long-term use, it can cause cognitive impairment and ADHD, so it is better to use other drugs in the

treatment of neonatal seizures. Comparison of Topiramate with Phenobarbital was not different in controlling neonatal seizures. Still, considering the side effects of Topiramate mentioned above, Topiramate does not seem to be preferable, although decisions can be made based on the case and possible side effects. A comparison of Italept with Phenobarbital was not significantly different in controlling neonatal seizures, which is preferable due to its lower side effects. Considering that most episodes require medical treatment and most seizures are not controlled with one drug, and due to the long duration of treatment with antiepileptic drugs and the need to control them, and given that the fewer drugs used, the better for the patient, so in choosing an adjunct drug to control refractory seizures, it is better to use a drug that is both effective and has fewer side effects and better tolerability.

One of the study's most critical shortcomings is that it examines only the electroencephalogram, ignores other interventions, does not measure blood levels, and lacks long-term follow-up of infants.

It is suggested that other drugs be examined in future studies, and a study with a similar subject to this study will evaluate the effect of the interventions used in this study on other patients with nervous system problems to compare with the findings of the present research to determine the scalability of the results accurately.

In Conclusion

Considering a need for anti-Seizure medications in most seizures, most seizures cannot be controlled with one drug. Choosing an adjuvant drug to control treatment-resistant seizures is essential because, in most cases, there is a need for control and a long duration of treatment with antiepileptic

drugs and less use is better for the patient, so it is better to use a drug that is both effective and has fewer side effects and better tolerance. According to the findings of this study and due to the same effect of Phenobarbital, Levetiracetam and Topiramate in the control of newborn seizures and the absence of complications, it seems that Topiramate and Levetiracetam were also used as drugs of choice in the control of neonatal seizures. Additionally, these drugs can be used to eliminate abnormalities related to children's brain paroxysmal discharges.

Future direction

It is suggested that the effect of the interventions used in this research on other patients or even other patients with nervous system problems be evaluated, and the findings of the current research should be compared so that the results can be generalized and specified precisely. Moreover, the administration of other drugs and long periods of follow-up (at least one year) are suggested.

Limitations

One of the crucial shortcomings of this research is that it only examines EEG and ignores other interventions and variables that affect infant seizures, such as not measuring blood levels.

In this research, the intervention was performed only on children with seizures, and its results cannot be generalized.

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The research was approved and registered in the Research Council of Tabriz Medical School with

the ethical code IR.TBZMED.REC.1398.1077 and also with IRCT 20200115046137N1 code.

Authors' Contribution

Islamian Leila: Collated and analysed data from the questionnaires used in phase one, performed the qualitative interviews, coded the data, performed initial thematic analysis, and reviewed the final draft of the paper.

Erabi Giso: Collated and analysed data from the questionnaires used in phase one, performed the qualitative interviews, coded the data, performed initial thematic analysis, and reviewed the final draft of the paper.

Mousavi Mirhadi : Helped conceive the idea for the study, wrote the questionnaire used in phase one reviewed the data, assisted with interpretation, and reviewed and revised the final draft of the paper.

Sadeghvand Shahram : Provided support and advice on analysis of the qualitative aspects of the paper and advised on presentation and explanation of methods and results during write-up. And reviewed and significantly revised the paper.

All authors reviewed the manuscript and approved it.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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