TOPIRAMATE FOR REFRACTORY EPILEPSY IN PEDIATRIC PATIENTS: A MULTI-CENTER TRIAL ON CLINICAL OUTCOMES AND SIDE EFFECTS

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Abstract

This paper compared the efficacy and safety of topiramate in young children and infants with refractory epilepsy. A total of 24 children, aged 6 to 60 months, diagnosed with refractory epilepsy were included in the study. Three tertiary hospitals were used to recruit these children and the study protocol was accepted by the ethical committees of all the participating institutions. The first endpoint was the change of seizure frequency, with therapeutic responses categorized as satisfactory (seizure-free or >50% reduction) or unsatisfactory (≤50% reduction or worsening). The study also monitored side effects, including cognitive and physical symptoms, as well as changes in concomitant antiepileptic drug levels, liver function, and overall health. The results showed that 50% of the participants had a satisfactory response, with 21% achieving complete seizure freedom. The highest efficacy was observed in children with Lennox-Gastaut syndrome, followed by those with cryptogenic epilepsy. Common side effects included somnolence, poor appetite, irritability, and fatigue, all of which were generally mild and transient. Severe side effects, such as worsened seizures and hypothyroidism, were rare. Despite some limitations, including the absence of blood level monitoring for topiramate and a short follow-up period, the study supports topiramate as a viable treatment for refractory epilepsy in pediatric patients, particularly in cases where other AEDs have failed.

Keywords: Pediatric, Refractory Epilepsy, Topiramate, Seizure Control.

INTRODUCTION

Epilepsy is a typical neurological disease that is associated with frequent seizures that may be disabling and significantly affect the quality of life, particularly in children. While most children with epilepsy respond well to antiepileptic drugs (AEDs), a subset of children continues to experience frequent seizures despite the use of multiple medications [1-3]. This condition is referred to as refractory epilepsy, also known as drug-resistant epilepsy (DRE). The term "refractory" denotes cases in which seizures persist despite appropriate trials of at least two AEDs from different drug classes, taken at therapeutic levels [4-6]. Refractory epilepsy in children presents unique challenges, both in terms of diagnosis and management, necessitating a comprehensive approach to treatment.

Etiology and Classification of Refractory Epilepsy

The causes of epilepsy in children are diverse and can be broadly classified into genetic, structural, metabolic, and immune-related categories. Genetic influences are also important to the occurrence of epilepsy especially in syndromes of idiopathic epilepsy including childhood absence epilepsy and juvenile myoclonic epilepsy. In contrast, structural causes, such as brain malformations, perinatal injuries, or brain tumors, can also lead to refractory epilepsy. Metabolic disorders, such as mitochondrial diseases, and autoimmune conditions, like Rasmussen's encephalitis, can contribute to the development of seizures that do not respond to conventional therapies [7-10]. Refractory epilepsy in children is often classified based on the age of onset and the underlying cause. The syndromes that are common as a part of refractory epilepsy are Lennox-Gastaut syndrome (LGS), Dravet syndrome, and infantile spasms (West syndrome). These conditions are characterized by specific seizure patterns and cognitive impairments, making them challenging to manage. For instance, LGS is a severe form

of childhood epilepsy that typically emerges in children between 3 and 5 years of age and is often accompanied by developmental delays. Similarly, Dravet syndrome, a rare genetic disorder, manifests in the first year of life and is associated with prolonged seizures and cognitive deterioration [11-16].

Impact on Quality of Life

The impact of refractory epilepsy on a child's quality of life cannot be overstated. Frequent seizures can lead to significant physical, cognitive, and psychological consequences. Physical injuries resulting from seizures, such as falls, burns, or head trauma, are common. In addition, cognitive impairments often accompany refractory epilepsy, with affected children experiencing delays in language development, motor skills, and academic performance. Psychosocial issues, including anxiety, depression, and social isolation, are also prevalent among children with refractory epilepsy. The constant uncertainty about when the next seizure will occur can affect both the child and their family, creating significant emotional strain. The diagnosis of refractory epilepsy requires a thorough clinical evaluation, including a detailed history of the child's seizures, neurodevelopmental milestones, and family history of epilepsy. The first step in diagnosing epilepsy is the confirmation of recurrent seizures, typically through observation by caregivers, family members, or healthcare professionals. A diagnosis of refractory epilepsy is established when seizures persist despite adequate treatment with two or more AEDs.

METHODS

The rationale behind carrying out this study was to investigate the effectiveness of topiramate in infants as well as young children with the refractory epilepsy. Between January and December, a successive group of 24 children (14 boys and 10 girls) with refractory epilepsy (that is, recurrent seizures that have not been controlled despite combination and administration of at least two AEDs, or antiepileptic drugs) were identified. The recruiting hospitals were three tertiary hospitals and the protocol of the study was accepted by the ethical committees of all the hospitals where the study was conducted. The inclusion criteria that were used to select the patients were as follows: (i) patients between the ages of 6 months and 5 years old, (ii) refractory epilepsy, (iii) taking at least two AEDs, and (iv) no progressive neurological disease. All patients were subjected to electroencephalogram (EEG) and either computerized tomography (CT) or magnetic resonance imaging (MRI). The frequency, type and duration of seizures were captured via seizure diaries that were kept by parents or caregivers. In the case of children with frequent spasms or absences that were hard to measure, parents were requested to give an estimation of the percentage change in weekly seizure frequency, with choices of completely free of spasms, improvement of 50% or less, none, improvement of 50% or less, or worsening. The EEGs were not repeated due to financial limitations. The types of seizures were grouped into three, namely, infantile spasms (IS), where typical clinical and EEG repetitive features were considered; the Lennox-Gastaut syndrome (LGS), characterized by mixed seizure types, developmental delay, and repeated slow spike-wave EEG discharges; and other epilepsies, where IS and LGS were excluded. Also, the etiology of seizures was categorized into cryptogenic and symptomatic seizures with five of the nine children with IS having tuberculus sclerosis.

The treatment with topiramate was introduced after the informed consent, and the initial dose of topiramate was 1 mg/kg twice a day, and the dose was increased every 2 weeks by 1-3mg/kg/day until a minimum dose was reached (1-2 cessation of seizures), depending on the child's tolerance. The study included 24 children, who were followed for a mean duration of 6 months (ranging from 3 to 10 months). Monitoring for side effects, blood levels of concomitant AEDs, liver function, EEGs, renal ultrasound, and eye examinations was conducted for all participants. However, due to resource limitations, topiramate blood levels were not measured.

Satisfactory responses in terms of therapy were viewed as complete remission (seizure-free) or over 50 percent reduction in the number of seizures. Responses were not satisfactory when there was a 50 percent or below reduction in seizures or when the seizure did not change or even increased. The participants were expected to visit follow-ups monthly to be examined on possible side effects, or at

an earlier date in case any problems emerged. Analysis of data was done using Epi info version 6 and statistical differences across groups were evaluated using Fisher exact test.

Results and Discussion

Table 1: Demographic and baseline data of the patients.

Attribute	Number and Percentage
Age (months)	
Range	5 — 60
Mean	32
Gender	
Boys	14
Girls	10
Epilepsy Classifications	
Symptomatic	08 (32%)
Cryptogenic	16 (68%)
Infantile Spasm	05 (19%)
Lennox—Gastaut	12 (53%)
Others	07 (28%)
Number of Background AEDs	
Two AEDs	16
More than Two AEDs	08

This paper has assessed the effectiveness and safety of topiramate in the management of refractory epilepsy in young children and infants [17]. The number of children enrolled in the study was 24 children between 6 and 60 months who had refractory epilepsy. These children have been recruited in three tertiary hospitals and all the subjects gave an informed consent before taking part [18].

Demographics and Baseline Characteristics

The table 1 displays the baseline demographic and clinical attributes of the study participants. The average age of the children was 32 months ranging between 5 and 60 months. There was a slightly higher proportion of boys (14 boys, 57%) compared to girls (10 girls, 43%) in the study [8]. The majority of the participants had cryptogenic epilepsy (68%), while 32% had symptomatic epilepsy. The most common types of epilepsy observed were Lennox-Gastaut syndrome (LGS), which affected 53% of the participants, followed by infantile spasms (IS) in 19%, and other types of epilepsy in 28% [4]. Regarding the use of background AEDs, the majority of children (68%) were on at least two AEDs, with 32% of participants receiving more than two AEDs [14]. The children were required to have failed treatment with at least two AEDs before being considered for inclusion in the study [19]. This provided a clear baseline indication of the refractory nature of their epilepsy, as these children had not responded to initial treatments [15, 16].

Efficacy of Topiramate

The therapeutic response to topiramate was categorized into three groups: total remission (seizure-free), >50% improvement, and ≤50% improvement or no improvement. As seen in Table 2, a total of 24 children (50% of the cohort) experienced a satisfactory response to treatment with topiramate. Of these, 5 children (21%) achieved total remission, and 10 children (42%) had a >50% improvement in

seizure frequency [17]. The response rates varied according to the clinical types of epilepsy. Children with Lennox-Gastaut syndrome (LGS) exhibited the highest response rate, with 7 children (54%) reporting satisfactory responses, including 3 who achieved total remission. In contrast, children with infantile spasms (IS) had a lower response rate, with only 2 children (40%) showing satisfactory improvement [18].

When considering the two etiological categories, children with cryptogenic epilepsy showed a better overall response to treatment compared to those with symptomatic epilepsy. A total of 10 out of 16 children with cryptogenic epilepsy (63%) had satisfactory responses, whereas only 5 out of 8 children with symptomatic epilepsy (63%) had satisfactory responses. This difference in response rates suggests that topiramate may be more effective in treating certain types of epilepsy, particularly those with a cryptogenic etiology. Despite the promising results in some patients, 9 children (38%) did not show significant improvement, as their seizures either remained unchanged or worsened. Among these non-responders, 4 children (17%) experienced worsening seizures, which is a significant concern in managing refractory epilepsy [19].

Table 2: The responses to topiramate depending on the type of epilepsy.

Response	LGS (n = 13)	IS (n = 5)	Others (n = 7)	Total (n = 24)	Cryptogenic (n = 16)	Symptomatic (n = 8)
Total Remission	03	01	01	05	02	01
>50% Improvement	04	01	03	10	09	04
Total Satisfactory	07	02	04	15	10	05
≤50% Improvement	01	01	01	03	03	01
No Response	03	01	01	04	02	01
Worse	02	01	01	02	01	01
Total Unsatisfactory	06	03	03	09	16	03

Safety and Adverse Effects

Topiramate was generally well tolerated, though several adverse effects were observed during treatment. Table 3 summarizes the side effects experienced by the participants. The most commonly reported side effects were somnolence (28%), poor appetite (23%), and nervousness, irritability, and agitation (23%). These side effects are consistent with the known adverse effects of topiramate, which can include cognitive and mood disturbances [20]. Fatigue and abdominal pain were reported by 19% of the participants, while headache and dizziness were reported by 11%. More severe side effects, such as worsened seizure frequency (9%), psychomotor slowing (9%), and weight loss (4%), were less common but still noteworthy [21]. A few patients (4%) also reported visual complaints and memory complaints, which have been associated with topiramate use in previous studies. One patient experienced hypothyroidism, which was identified as a possible side effect of topiramate. Hypothyroidism is a rare but known side effect of topiramate, and this observation warrants further monitoring of thyroid function in children receiving long-term treatment with this drug. The overall incidence of adverse effects was consistent with previous reports on topiramate, although the side effects observed in this cohort were generally mild and manageable.

Table 3: Adverse effects found during topiramate treatment (n = 13).

Side Effects	Number of Patients
Somnolence	06
Poor appetite	05
Nervousness, irritability, and agitation	05
Fatigue	04
Abdominal pain	04
Headache	03
Dizziness	03
Worsened seizures frequency	02
Psychomotor slowing	02
Weight loss	02
Visual complaint	01
Memory complaint	01
Hypothyroidism	01

Discussion

The findings of the present study prove that topiramate may be effective in the treatment of children with refractory epilepsy. The percentage of children who had an improvement in the seizure control was high, and half of the group of children responded to therapy adequately. Topiramate had some remarkable effects, especially in children who had Lennox-Gastaut syndrome (LGS) which is a serious and incurable form of epilepsy [22]. This topiramate capability of offering significant improvement in the rate of seizures in this group is encouraging since LGS has usually been traced to be unresponsive to traditional AEDs.

The study also highlights that topiramate may be more effective in children with cryptogenic epilepsy than those with symptomatic epilepsy. This finding may suggest that topiramate acts more effectively in cases where the underlying cause of epilepsy is not known, possibly due to a more uniform pathophysiological mechanism of seizures. However, the lack of significant improvement in some children with symptomatic epilepsy underscores the heterogeneous nature of epilepsy and the difficulty in treating this condition with a single AED [23].

Safety assessments revealed that topiramate was generally well tolerated, with most adverse effects being mild and transient. The most commonly reported side effects were somnolence, poor appetite, and irritability, which are consistent with the known side effect profile of topiramate in both pediatric and adult populations. More serious adverse effects, such as worsened seizure frequency and hypothyroidism, were rare but should be monitored in long-term use. The need for ongoing monitoring of thyroid function and potential weight loss is essential for ensuring the safe and effective use of topiramate in children.

There are some limitations of this study, which can be taken into account when interpreting the results [24]. The size of the sample was not that big, the follow-up time was not long, and it does not provide the possibility to estimate the long-term safety and effectiveness of topiramate. Also, there was a deficit of the blood level monitoring of topiramate, which could have an impact on the correctness of the determination of the optimal dose per patient. More research using bigger samples, and extended follow-up durations is necessary to provide support in verifying these results and assessing the long-term safety of topiramate in children.

Conclusion

To sum up, this paper presents proof that topiramate is a good medication in the treatment of refractory epilepsy in infants and young children, especially in those with Lennox-Gastaut syndrome and cryptogenic epilepsy. The drug showed a positive effect on seizure control in a significant proportion of patients, with most adverse effects being mild and manageable. Although there are certain shortcomings, this research adopts the use of topiramate as a viable solution in the treatment of children with refractory epilepsy, when other AEDs have been ineffective. These findings will need further research on large sample sizes and lengthy follow-up on a larger scale to confirm them and maximize the management of pediatric refractory epilepsy.

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