

# The efficacy and safety of Topiramate in the Treatment of Refractory Epilepsy in children in Paediatric Neurology clinic at Izzat Ali Shah Hospital

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## Author's Contribution

<sup>1,6</sup> Conception of study

<sup>1</sup> Experimentation/Study conduction

<sup>1,3</sup> Analysis/Interpretation/Discussion

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## Abstract

**Objectives:** This study has been performed to observe the efficacy & safety of Topiramate in refractory epilepsies in children in Pakistan.

**Materials and Methods:** A cross-sectional prospective consecutive series of children age between (1-14 years) with refractory epilepsy were recruited from the Paediatric Neurology clinic of Izzat Ali Shah Hospital. Epilepsy was classified into Generalized, Focal, and Unknown based on ILAE Classification. Topiramate was added in patients who were refractory to at least two anti-epileptic drugs. The outcome was recorded in four categories i.e total remission, >50% seizure reduction, <50% seizure reduction, and no improvement.

**Results:** Fifty-eight patients were enrolled in the study, but 5 patients were dropped out due to significant side effects. Most of the children were in the age group ranging from 5 to 10 years with predominant boys (n=32). The major type of epilepsy was 53% (n=28) was Unknown, while 36% (n=19) children had Generalized epilepsy and 11% (n=6) had Focal epilepsy. 25% children had total remission, 38% had >50% seizure reduction, 28% had < 50% seizure reduction and 9% had no improvement. Total remission was mostly seen in Focal epilepsy (50%) and least shown in Unknown type (14%) and the difference was significant (Chi-Square test p=0.039). Adverse effects to Topiramate were found in 33 (62%) of the total enrolled patients. Common adverse effects were weight loss in 14(26%), poor appetite in 13(24.5%), and behavioral issues in 6(22.5%) children.

**Conclusion:** Topiramate is an effective anti-epileptic drug (AED) in refractory epilepsy especially with Focal and Generalized onset but is not as effective in other types of Refractory epilepsy. Weight loss and poor appetite were the commonest adverse effects that were reversible after dose reduction.

**Keywords:** Focal epilepsy, Generalized Epilepsy, Refractory Epilepsy, Topiramate.

## Introduction

Topiramate is mainly an anti-epileptic drug (AED) which is a carbonic anhydrase inhibitor. Topiramate is a 2,3:4,5-di-O-isopropylidene- $\beta$ -D-fructopyranose sulfamate compound.<sup>1</sup> It acts by blocking sodium channels, enhancing GABA-induced influx of chloride, and inhibiting kainate/AMPA glutamate receptors.<sup>2,3</sup> Topiramate is well absorbed orally. It is not extensively metabolized & is eliminated unchanged in the urine. Hence, it indicates that urinary excretion is a major route of excretion. Chronic renal and hepatic impairment can affect the clearance of Topiramate.<sup>4</sup>

It is clinically used for a different type of epilepsy but has an important role in infantile spasms and Lennox-Gastaut syndrome. It is also used in the prevention of Migraines, Bipolar disorder, Schizophrenia, Bulimia nervosa, binge eating disorders, alcohol dependence, weight loss, mood instability disorder, obesity, etc.<sup>5-7</sup> Spritzer et al analyzed the literature and concluded that Topiramate is also effective in patients having both Epilepsy and Migraine.<sup>8</sup> Topiramate can be given alone or in combination with other drugs in Generalized Tonic-Clonic seizures or Focal seizures.<sup>9</sup> Topiramate can have drug interactions with Phenytoin, Valproic acid, and Carbamazepine. Some patients attain higher Phenytoin serum levels when Topiramate is added to their drug regime. On the other hand serum Topiramate levels may be reduced when given with Phenytoin and Carbamazepine. Marques et al monitored the plasma concentration level of Topiramate in patients with epilepsy and found it below the therapeutic range in 83% of patients. Antiepileptic drug inducers tend to reduce their plasma concentration, hence increases the risk of seizures.<sup>10</sup>

Refractory Epilepsy is uncontrollable, intractable, or drug-resistant epilepsy, which is the failure of adequate trials of at least two tolerated and appropriately chosen anti-epilepsy drugs (AEDs) to achieve sustained seizure freedom for a sufficiently long period of time.<sup>11</sup> The incidence of refractory epilepsy in developed countries is 6 per 1000 patients of epilepsy but it ranges from 7% to 35% and a greater range is more applied to children.<sup>12</sup> There is no data available regarding its incidence in the Pakistani population. The cause of refractory epilepsy is often not known. There are very few studies reported regarding the efficacy of Topiramate in refractory epileptic children. Kanner et al reviewed 13 years of literature for refractory epilepsy treatment and

suggested treatment guidelines in adults and children. Topiramate was mainly recommended in Focal epilepsy.<sup>13</sup> Asadi-pooya et al described a comprehensive review of Lennox-Gastaut Syndrome (LGS) and considered Topiramate as the first-line treatment for LGS along with Valproate and Lamotrigine.<sup>14</sup> Gomes et al proposed the treatment protocol for the super-refractory status epilepticus and suggested Topiramate with other anti-epileptics along with anesthetic medicines.<sup>15</sup>

This study was designed to assess the effectiveness of Topiramate in children with refractory epilepsy in Pakistan as no previous studies are reported in this region.

## Materials and Methods

The primary objective was to observe the efficiency & safety of Topiramate in refractory epilepsies in children in Pakistan.

**Study Design and settings:** A cross-sectional prospective consecutive series of children age between (1-14 years) with refractory epilepsy were identified from January 2019 to December 2020. The children were recruited from the Paediatric Neurology clinic of Izzat Ali Shah Hospital.

Patients were selected according to the following criteria: (i) age between 1-14 years. (ii) Refractory epilepsy (iii) currently on two or more AEDs. Electroencephalograph (EEG) & Computerized Tomography (CT) or MRI Brain was performed in all patients. Epilepsy was classified into three categories according to ILAE 2017 Operational Classification. (i) Generalized Epilepsy (ii) Focal Epilepsy and (iii) Unknown.

Verbal consent was obtained from the caregivers. Topiramate was started at the daily dose of 1 mg/kg followed by 2 weekly increments up to a maximum daily dose of 10 mg/kg at all ages. If a child was not able to tolerate, developed fever or extreme lethargy after starting the Topiramate then he/she was excluded from the study, and Topiramate was stopped. With minor side effects listed in Table 2, the study was continued. Parents or caregivers were asked to record the change in seizure duration and frequency. All the children were followed up for a mean period of 3-6 months. Responses were recorded according to the following four categories. (i) Complete remission (ii) >50% seizure reduction (iii) <50% seizure reduction (iv) No improvement. All the results were recorded in predesigned proforma. Patients were asked to attend the hospital anytime if

any side effect occurred. Side effects were also recorded during follow-up visits. The collected data was analyzed using SPSS version 25.

## Results

Fifty-eight children were enrolled in the study. Five patients were dropped out from the study due to significant side effects. Their demographic characteristics are mentioned in Table 1. Most of the children (n=27) enrolled had an age range between 5 to 10 years with predominantly boys (n=32). The major type of epilepsy 53% (n=28) was Unknown, while 36% (n=19) children had Generalized epilepsy and 11% (n=6) had Focal epilepsy. Most of the children (87%) were receiving more than two AEDs.

The response of Topiramate is given in Table 2 where 25% of children had total remission, 38% had >50% seizure reduction, 28% had < 50% seizure reduction and 9% had no improvement yet there was no case with a worse response. Total remission was mostly seen in Focal epilepsy (50%) and least shown in Unknown types (14%). More than 50% seizure reduction was seen in all types of epilepsy. Less than 50% improvement was mostly seen in unknown types. In children with Generalized refractory epilepsy, there was a satisfactory response (total remission plus >50% seizure reduction) to Topiramate in 15 of our 19 cases. In children with Focal epilepsy, there was a satisfactory response to Topiramate in 5 out of 6 cases. According to the correlation between types of epilepsies and their responses, the difference is significant (Chi-Square test  $p=0.039$ ). Table 3 shows the

clinical response to Topiramate according to age categories. Ages between 1 to 10 years showed better response than age between 11 to 14 years but it was not statistically significant ( $p=0.216$ ).

Adverse effects to Topiramate are mentioned in Table 4 and were found in 33 (62%) of the total enrolled patients. Some of adverse effects were seen in children like somnolence in 2 (3.5%), poor appetite in 13(24.5%), behavioral issues in 6(22.5%), fatigue in 1(2%), fever in 5(9%), psychomotor slowing in 1(2%), weight loss 14(26%), sleep disturbances in 4(7.5%) & others in 2(3.5%).

**Table 1: Demographic & baseline characteristics of patients receiving Topiramate**

Attribute	Number (n=53)	Percentage (n%)
<b>Age Range (years)</b>		
1 to 5	29	54%
6 to 10	17	32%
11 to 14	7	13%
<b>Gender</b>		
Boys	32	60.5%
Girls	21	39.5%
<b>Epilepsy classification</b>		
Generalized	19	36%
Focal	6	11%
Unknown	28	53%
<b>Number of background AEDs</b>		
Two AED	7	13%
More than 2 AEDs	46	87%

**Table 2: Responses to Topiramate according to the clinical types of epilepsy**

Type of Epilepsy	Total remission	>50% seizure reduction	<50% seizure reduction	No seizure improvement	P value
Generalized (n=19)	6 (32%)	9 (47%)	3 (16%)	1 (5%)	0.039
Focal (n=6)	3 (50%)	2 (33%)		1 (17%)	
Unknown (n=28)	4 (14%)	9 (32%)	12 (43%)	3 (11%)	
Total (n=53)	13(25%)	20(38%)	15(28%)	5(9%)	

**Table 3: Response to Topiramate according to age categories**

Age Categories	Total remission	>50% seizure reduction	<50% seizure reduction	No seizure improvement	P value
1-5 years (n=29)	7(24%)	12(41%)	8(28%)	2(7%)	0.216
6-10 years (n=17)	4(23%)	8(48%)	5(29%)	0	
11-14 years (n=7)	2(29%)	0	2(29%)	3(42%)	
Total (n=53)	13(24%)	20(38%)	15(28%)	5(1%)	

**Table 4: Side effects observed during treatment with Topiramate (n=33)**

Side effects (33 patients)	Number of patients	Percent
Somnolence	2	3.5%
Poor appetite	13	24.5%
Behavioral issues	6	11%
Fatigue	1	2%
Abdominal pain	-	-
Headache	-	-
Fever	5	9%
Psychomotor slowing	1	2%
Dizziness	-	-
Weight loss	14	26%
Visual complain	-	-
Memory complain	-	-
Sleep disturbance	4	7.5%
Others	2	3.5%

## Discussion

This study shows that Topiramate is effective and well-tolerated in infants and children with Refractory epilepsy. The response was more satisfactory in a focal and generalized type of epilepsy as compared to the unknown category.

In a quite similar study, Al Ajlouni et al reported that 60% of children with Refractory epilepsy showed a satisfactory response (total and more than 50% remission) while the remaining 40% showed an unsatisfactory response.<sup>16</sup> Hassan et al reported that 34% of children with uncontrollable seizures became seizure-free and 39% achieved more than 50% reduction in seizure frequency.<sup>17</sup> Ritter et al reported >50% reduction in symptom frequency in 57% of children with Partial epilepsy, and 14% became seizure-free.<sup>18</sup> Coppola et al achieved seizure-free status in 20% of children with Refractory Partial epilepsy and 45% of patients had a 50% reduction in seizure frequency.<sup>19</sup> Biton et al achieved >50% reduction in their seizure frequency in 46% of children with primary generalized epilepsy compared to the 17% in the placebo control group.<sup>20</sup> Glauser et al concluded that 15% of children with Lennox Gastaut syndrome showed total improvement while 55% had more than 50% reduction in seizure frequency.<sup>21</sup> Kato et al compared the efficacy and tolerability of Topiramate, Lamotrigine, and Levetiracetam in children with Refractory epilepsy. A total of 55 children received Topiramate, 44 children had Lamotrigine, and 38 received Levetiracetam. He

concluded that Levetiracetam was the most effective drug in Refractory childhood epilepsy with partial and Generalized epilepsy, while Topiramate was effective in Partial epilepsy and Lamotrigine in Generalized epilepsy.<sup>22</sup> Unalp et al concluded that 51 children (72%) showed a good response to initial treatment but a loss of efficacy in long-term use occurred in 17 (33.3%) of initial responders.<sup>23</sup> Liu et al studied that Topiramate is effective both as monotherapy and add on therapy in post-operative neurosurgical patients.<sup>24</sup> It is also recommended that in younger children dosage may be adjusted according to response rather than using the absolute Topiramate dose. It is, therefore, possible that higher doses (>10mg/kg/day) may prove to be more effective in the future.<sup>25</sup> As shown in Table 3, most of the side effects of Topiramate were minor and the drug was well tolerated. Side effects were noted in 62% of patients, the most common side effects in our study were loss of appetite, weight loss, and behavioral issues and the least common was psychomotor slowing which was noticed in only one child in our study. As compared to other studies we experienced fewer cognitive side effects. Some of our patients also complained of fever which resolved spontaneously. Most of the side effects were transient which resolved spontaneously or with dose reduction. In Al Ajlouni's study, the most common side effects were Somnolence, Poor appetite, and Irritability.<sup>16</sup> Coppola et al suggested Topiramate as the first choice in the treatment of generalized epilepsy but highlighted the side effects related to cognition and memory.<sup>26</sup> Our study didn't record any such adverse effects.

## Conclusion

In this study, it is concluded that Topiramate is an effective AED in Refractory epilepsy especially with Focal and Generalized onset but it is not as effective in other types of Refractory epilepsy. Weight loss and poor appetite were the commonest adverse effects that were reversible after dose reduction. Topiramate is a worthy option for children with high seizure frequency refractory to standard AEDs.

This study did not compare Topiramate with other drugs in refractory epilepsy and it is recommended that further comparative studies may be conducted to see the effectiveness of Topiramate in different types of epilepsies.

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