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Efficacy and Safety of Topiramate as Monotherapy in Treatment of Partial Epilepsy in Children: A Randomized Controlled Trial

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Abstract

Background: Partial epilepsy is more common among children. **Objective:** The aim of the study was to compare the efficacy and safety of Topiramate (TPM) to previously recommended drug Carbamazepine (CBZ) in the treatment of partial epilepsy. **Methodology:** This randomized controlled trial was conducted in outpatient department of Pediatric Neurology at National Institute of Neurosciences and Hospital (NINS&H), Dhaka, Bangladesh during the period of July 2017 to December 2017. Children with the age group of 0 to 18 years who were diagnosed as newly onset partial epilepsy were randomized into study group (TPM) and control group (CBZ). The efficacy and safety of TPM was evaluated after 6 months of treatment. **Results:** A total number of 50 children were recruited for this study. The primary outcome was assessed in 50 children by measuring frequency of seizure before and after treatment. Seizure frequency decrease significantly after treatment with both drugs where TPM group was 5.21±2.96 to 1.80±0.94 and CBZ group was 6.83±4.88 to 1.80±1.0/month respectively ($p < 0.001$). **Conclusion:** Topiramate is effective and safe in the treatment of partial epilepsy in children. *[Journal of National Institute of Neurosciences Bangladesh, January 2022;8(1): 14-18]*

Keywords: Topiramate (TPM); monotherapy; partial epilepsy; efficacy

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Introduction

Epilepsy is a common neurological condition in which abnormal electrical discharges from brain causes recurrent unprovoked seizure[1]. National epilepsy survey in Bangladesh by WHO found that partial epilepsy is more common about 11.5 per 1000 population in children which is about 30.6% of total epilepsy. About 70.0% individuals with active epilepsy have become seizure free and achieve remission with a single antiepileptic drug (AED)[2]. NICE guidelines recommended monotherapy for treatment of epilepsy both in adult and children when it is possible (NICE 2012). Remaining 30% become refractory or drug resistance seizures. They need combinations of AEDs or alternative therapies, such as epilepsy surgery[3]. Appropriate selection of first line antiepileptic drug for newly diagnosed seizure is the key of management of epilepsy[4].

Carbamazepine (CBZ) was older AED and frequently used as monotherapy for partial or generalized onset seizures for over 30 years[5]. Topiramate (TPM) is a 'second-generation' AED, used as monotherapy for

epileptic seizures after proven efficacy in dose-controlled studies compared with carbamazepine and sodium valproate[6]. Epilepsy is a burden to the society. Optimal management improves health outcomes and can help to minimize other, often detrimental, impacts on social, educational and employment activity. Bangladesh is a densely populated country, of which 31% are children. Epilepsy is common in children about 8.6/1000 population. In a recent nationwide epilepsy survey it was found that partial epilepsy is more common about 11.5/1000 population in children, which is about 30.6% of total epilepsy in children, according to National epilepsy survey in Bangladesh by WHO (unpublished). Carbamazepine (CBZ) and oxcarbazepine are two recommended drug for treating partial epilepsy (ILAE, AAN, NICE). The life threatening side effects of CBZ is Steven Johnson syndrome which is 60 cases out of 100,000 but another recommended drug is topiramate (TPM) which has minimum side effect profile and currently available in our country. So the intention of our study is to compare the efficacy and side effects (if any) of TPM compared to previously recommended drug (CBZ) in the treatment of partial epilepsy.

Methodology

Study Settings and Population: This was a randomized controlled trial done at the outpatient department of Pediatric Neurology, National Institute of Neurosciences & Hospital (NINSH), Dhaka, Bangladesh from July to December, 2017 for a period of 6 months. Children who were diagnosed with new onset partial seizure (simple partial, complex partial) of Pediatric age group (0 to 18 years) of both sexes and who had not history of other seizure type (GTCS or absence or myoclonic) in addition to partial epilepsy and not taking any drug for epilepsy as well as who were intended to be enrolled were randomized either as case (TPM treatment group) and control (CBZ treatment group). Prior to beginning of the study the research protocol was accepted by ethical review committee of NINS & H (ERC no-36) and informed written consent was taken from parents.

Randomization and Blinding: Randomization was done by lottery method with single blinding.

Allocation: Children were evaluated thereafter thorough detail history, clinical examination, biochemical parameters and EEG was done in every children. Initial starting dose was 5 mg/kg at night for CBZ and for TPM (2 mg/kg), given for 1 week. Then the drug was titrated by 5 mg/kg at 2 weeks interval, for CBZ up to 20 mg/ kg as a maintenance dose and TPM was titrated up to 5 mg/kg as maintenance dose two weekly.

Follow up and Outcomes Measures: Patients were followed at 2 weeks, 1month, 3 month and 6 month of starting of treatment. Primary end point of the study was 6 months after treatment to find out the efficacy and safety of both TPM and CBZ. Any untoward effects of drugs were also recorded.

Statistical analysis: Statistical analysis of the study was done by using the Statistical Package for Social Science (SPSS) version 22.0. The result was presented in tables, figures and diagrams. Confidence interval was considered at 95% level. The qualitative data was expressed as frequency and percentage and the quantitative data was expressed as mean with standard deviation. Chi-square test and Fisher's Exact test was performed to compare between qualitative variables. Probability value less than 0.05 was taken as statistically significant.

Results

The present study intended to see the efficacy of carbamazepine (CBZ) and Topiramate (TPM) in the treatment of partial epilepsy in children aged 0 to 18 years. In this study 50 children were randomly assigned into two groups among which 25 children were treated with CBZ and 25 children were treated with TPM. The primary outcome variable was decrease frequency of seizure before and after treatment. There was no significant difference between the two treatment groups in terms of age and sex (Table 1).

Table 1: Demographic Profile of the Patients among Study Population (n=50)

Variables	Intervention Group	Control Group	P value
Age Group			
• 1 to 5 Years	10 (40.0%)	8 (32.0%)	
• 6 to 10 Years	11 (44.0%)	10 (40.0%)	
• 11 to 15 Years	4 (16.0%)	7(28.0%)	
Mean±SD	6.71 ± 2.80	6.99 ± 3.46	*0.751
Gender			
• Male	15 (60.0%)	14 (56.0%)	**0.774
• Female	10 (40.0%)	11 (11.0%)	
Age of onset of seizure (years)	5.42 ± 3.06	3.89 ± 3.86	*0.128

*Unpaired t test and **Chi-square test was done to measure the level of significance

Frequency of seizure measured by average seizure per month in individual cases before starting treatment were 6.83±4.88& 5.21±2.96 in CBZ and TPM group respectively. At 4th follow up the frequency was

decreased to 1.80±1.06 and 1.86±0.94 and p value was significant (0.001) (Table 2).

Table 2: Frequency of Seizure before and after Treatment in Two Groups (n=50)

Outcomes	Intervention Group	Control Group	P value
Before treatment	5.21 ± 2.96	6.83 ± 4.88	[a]0.180
After treatment			
1st follow up (2wks)	4.40 ± 2.70	5.43 ± 4.97	0.669
2nd follow up (1mon)	5.00 ± 3.18	3.86 ± 2.61	0.226
3rd follow up (3mon)	3.00 ± 1.47	2.57±1.34	0.292
4th follow up (6mon)	1.86 ± 0.94	1.80 ± 1.06	0.837
P value (before treatment vs at 4th follow up)	0.001	0.001	

*Unpaired t test was done to measure the level of significance

After 6 month follow up it was found that more than 90.0% cases seizure reduction occurred more in CBZ than TPM group but p value (0.889) was not significant pointing towards similar efficacy for the studied drug (Table 3).

Table 3: Outcome after 6 months of Treatment in Two Groups (n=50)

Response	Intervention Group	Control Group	P value
No response	2 (8.0%)	1 (4.0%)	
>25.0 to 50.0%	11 (44.0%)	13 (52.0%)	
>50.0 to 90.0%	6 (24.0%)	6 (24.0%)	0.889
>90.0%	6 (24.0%)	5 (20.0%)	

Chi-square test was done to measure the level of significance

Common adverse reaction was skin rash, nausea, vomiting in CBZ group, and increase body temperature in TPM group. There was no significant difference (p=0.541) between two groups (Table 4).

Table 4: Adverse Events of Drugs in Two Groups (n=50)

Adverse Effect	Intervention Group	Control Group	P value
Nausea	0 (0.0%)	1 (4.0%)	
Anaemia	0 (0.0%)	1 (4.0%)	
Loss of appetite	1 (4.0%)	1 (4.0%)	0.541
Body temperature	1 (4.0%)	0 (0.0%)	
Weight loss	1 (4.0%)	0 (0.0%)	
Rash	0 (0.0%)	1 (4.0%)	

Chi-square test was done to measure the level of significance

Discussion

Epilepsy is a common neurological condition in which abnormal electrical discharges from brain causes recurrent unprovoked seizure[1]. There are two main types of seizure, focal and generalized[2]. Carbamazepine was amongst the earliest of the traditional drugs, licensed for the treatment of epileptic seizures and has been commonly used as monotherapy for partial-onset seizure[3-4]. Topiramate is a second-generation AED, licensed as monotherapy for epileptic seizures following demonstrations of efficacy in dose-controlled studies compared with 'traditional' AEDs such as carbamazepine and sodium valproate[5-6].

This is a randomized control trial study which was done over 6 month period at outpatient department of pediatric neurology department at National Institute of Neurosciences and Hospital, Dhaka to compare the efficacy of topiramate as a monotherapy in case of partial epilepsy of children in respect to carbamazepine.

According to selection criteria 50 patient were enrolled. Every patient came to regular follow up and were analyzed. In this study basic demographic data such as age, sex, and weight were comparable both in study and control group. In this study mean age of the patients was 6.99±3.46 in CBZ group and 6.71 +2.80 in TPM group which was consisted with other studies[6-8].

In this study male predominance in both group is reported. Male were 14(56%) cases, 15(60%) cases and Female were 11(11%) cases and 10(40%) cases respectively. Other studies also found this type of male predominance than female that are also similar to our study[9-11]. The reason for male predominance may be due to more attention of family members.

In this study some important clinical variables were evaluated. Among them we observed mean age of onset of seizure 3.89±3.86 in CBZ group and 5.42±3.06 in TPM group, which is consistent with other studies[12-13].

In this study it was found that 32.0%children has h/o perinatal asphyxia in CBZ group and (52%) in case of TPM group, developmental delay present in 20.0% cases and 12.0%CBZ and TPM group respectively[13-15]. Other studies showed mainly of meningitis, stroke are associated features and this is not consistence with the present study[16-17]. Reason for this may be due to lack of hospital delivery and ignorance.

In this study, it is shown that frequency of seizure before treatment, it was 6.83+3.88 and 5.21+2.96 in both the group per month but decreases after treatment about 1.80+1.06 and 1.86+.94 respectively which was statistically significant. Another study showed that average 12 seizure occur per month in both groups[18-19].

Main outcome variables like reduction of frequency of seizure, response to drug and adverse events were evaluated in this present study. At the end of the 3

months follow up it was found that no response occur in case of 20% cases of CBZ group and 12.0% cases in TPM group. About 20.0% children developed more than 50.0% seizure reduction in CBZ group and in TPM group it was 28.0%, more than 90.0% reduction of seizure frequency occur in CBZ group (20.0%) and (16.0%) in TPM group that is almost same and p value was not significant (p value 0.803). Which was not consistent with other studies[20-21] one study showed that after 3 months response to TPM was favourable[22]. It may be due to non-compliance of the drug.

At the end of 6 months follow up it was found that more than 90.0% reduction of seizure also more in CBZ group than in TPM group but it was not statistically significant (p=0.889) which is consistent Cochrane database review[23]. By comparing the effectiveness of TPM and CBZ in partial epilepsy adverse events profiles are very low. In this study it was fond that in CBZ group 16.0% and in TPM group 12.0% patient shows adverse effects. Adverse effects are nausea (4.0%), anaemia (4.0%) and rash (4.0%) in CBZ group and increase body temperature and loss of weight (4.0%) in TPM group. Both groups of patient shows loss of appetite (4.0%)[24-25]. For this events no need to discontinue the treatment. In another RCT study similar adverse event that is nausea, weight loss, increase body temperature occurred but higher events of dizziness and fatigue in their study which was not consistent with our study[13]. The strength of the trial was that treatment was randomized. Other strength was the complete follow up of 50 children for the primary outcome. EEG was done for documentation with clinical seizure.

Conclusion

The current study has demonstrated that both the drugs are equally effective in treatment of childhood partial epilepsy with no significant untoward effects. Multicenter, double blinded, larger sample size, longer duration study from various ethnic group should be carried out.

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