

Evaluation of Cognitive Effects of Topiramate and Oxcarbazepine in Children with Epilepsy

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Abstract:

Epilepsy is the most common cause of morbidity in children worldwide, 80% of whom live in developing countries. It is the most common pediatric neurological disorder. The study was conducted on children with epilepsy of age from 1 to 15 years, attending in the paediatric neurology unit, Bangabandhu Sheikh Mujib Medical University (BSMMU). Available clinical records of cognitive function of children with epilepsy who were on topiramate for at least 6 months were compared with the children who were on OXC. Cognitive function of children on AEDs was also compared with that of epileptic children who will not be on AED. We evaluated the cognitive effects of TPM compared with oxcarbazepine (OXC), a drug that does not appear to affect cognitive function. Cognitive tests and subjective complaints of 20 patients with TPM monotherapy (1-9mg/kg/day) were retrospectively compared with those of 20 patients with OXC monotherapy at 6 months of medication. The two groups did not differ with respect to epilepsy-relevant variables or on baseline neuropsychological tests. The TPM group showed a significant difference in the performance of delayed word recall ($P < 0.05$). These cognitive effects shown in the TPM group were dose-related. The

cognitive dysfunction was trivial with patients taking TPM. OXC group did not show a significant difference in the performance of delayed word recall ($P < 0.05$). TPM has a negative effect on working memory and verbal fluency compared with OXC. It can be demonstrated at 1 year of treatment.

Key words: Cognitive, Topiramate, Oxcarbazepine

INTRODUCTION

Epilepsy is the most common cause of morbidity in children worldwide, 80% of whom live in developing countries¹. It is the most common pediatric neurological disorder². The reported age-specific incidence rates for childhood epilepsy vary considerably among different countries ranging from 39 to 134 cases per 100,000. In a population based study the prevalence rate of childhood epilepsy was distributed from 5.3 to 8.8 per 1,000³. Very little is known about childhood epilepsies in Bangladesh. In Bangladesh epidemiological surveys confirm that seizure disorders are common, one study showing prevalence rate of 68 out of every 1000 for 'any seizure history' and 9 out of every 1000 for 'any unprovoked seizure', in children aged 2 to 9 years⁴. This disorder can be successfully controlled with a single well-tolerated anti-epileptic drug (AED) in most cases. The treatment gap i.e. the percentage of those with epilepsy who are receiving no or inadequate treatment, is 90% in developing countries,⁵ 70% in rural India⁶ and 57% in South African children.⁷ Choice of right AED and its easy availability can substantially reduce the treatment gap. Topiramate & Oxcarbazepine has become WHO's 2nd line AED for partial and generalized tonic - clonic seizures in developing countries by virtue of its less side effects, efficacy and suitability.⁸⁻⁹

Cognition comprises a broad range of functions, such as attention, intelligence, visual memory, and fine motor dexterity. Abnormalities in cognition are commonly reported in child with

epilepsy. Problems with cognition can be manifested as reductions in attention, IQ, language and perceptual skills, executive functions including problem solving, verbal and visual memory, motor speed, dexterity, and coordination. The poorest cognition is associated with early age at onset and longer duration of epilepsy, especially in the presence of generalized tonic-clonic seizures, repeated episodes of status epilepticus, and increased exposure to antiepileptic drugs (AEDs)¹⁰. Several studies have suggested that antiepileptic drugs (AEDs) may impair cognitive function¹¹⁻¹⁶. Studies have shown that 30-50% of children treated with TPM experience cognitive side effects,¹⁷⁻²⁰ and one study showed a persistent reduction in IQ²¹. Others have found no such effect²²⁻²⁴. OXC is a newer antiepileptic drug with very few side effects. No study about cognitive function of OXC is done. So, it is justified to conduct studies to evaluate the cognitive effects of commonly used AED, topiramate and oxcarbazepine.

MATERIALS AND METHODS:

A randomized control trial was conducted to evaluate the long term impact of topiramate and oxcarbazepine on cognitive function in children with epilepsy at Pediatric Neurology Unit, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. All children (age 1-15 years) with epilepsy or those were presented with recurrent a febrile seizures during the study period were considered as study population. According to the selection criteria more than 100 cases were enrolled in our study. From this collection of documented cases we selected subjects if they matched all of the following criteria: (1) TPM or OXC monotherapeutic patients who were undergoing follow-up cognitive evaluations at 6 months, (2) TPM dosage less than 1-9 mg/kg/day, (3) either newly diagnosed epilepsy or had epilepsy that had not been treated with AEDs for more than 6 months, (4) no progressive

neurological disorders, head injury, mental retardation, alcohol or drug abuse, ongoing use of any central-acting medications, severe psychiatric problems, or other severe medical disorders, and (5) no cognitive complaints at baseline. In total, 20 patients for TPM therapy and 24 for OXC met the above criteria, with 20 of the latter patients being age-matched with the TPM group to form a comparison group. Patient characteristics are listed. Daily TPM dosages at 6 months were 1-9 mg/kg/day. Daily OXC dosages at 6 months were 10-20 mg/kg/day. Both groups showed a significant decrease of Equal 20 patients treated with topiramate and oxcarbazepine for at least 6 month were enrolled in the study. Cognitive tests were administered in a sound-attenuated, temperature-controlled room. All the tests were performed by a single examiner. According to the literature and our own clinical experience, we selected a few cognitive measures as being particularly sensitive to AED-induced cognitive impairment. We assessed memory function through list learning, immediate and delayed word recall, word recognition, and visual reproduction based on the Memory Assessment Scale, obtained from Psychological Assessment Resources. We assessed attention deficit by using (i) Bailey scale of infant development (BSID) (ii) Wechsler Preschool and Primary scale for intelligence (WPPSI-III^{uk}) (iii) Wechsler intelligence scales for children-revised (WISC-R). We examined attention, visuomotor tracking abilities, and mental flexibility by using the Trail Making Test (TMT) from the Halstead-Reitan Battery. We studied verbal fluency by using semantic fluency tests. Testing sessions lasted about 30 minutes. In the rare case of seizures occurring during neuro psychological examination, testing was suspended and data were not evaluated. We evaluated the differences in cognitive function, on the basis of subjective complaints and cognitive tests, between the TPM and OXC groups at 6 months.

RESULTS:

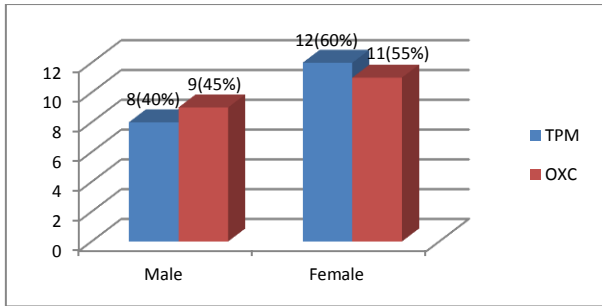
A) Demographic Characteristic

Table-A.1: Mean age among the study patients.

Age		
Group	Mean	Std. Deviation
TPM (n=20)	31.6	15.59
OXC (n=20)	32.6	14.58

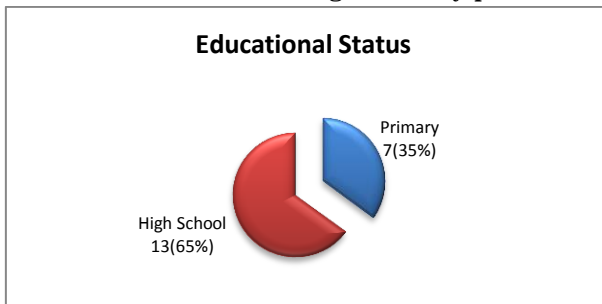
The table shows that the mean age of TPM group was 31.6(15.59) and group OXC was 32.6(14.58). This difference was not significant.

Figure-A.1: Sex distribution among the study patients.



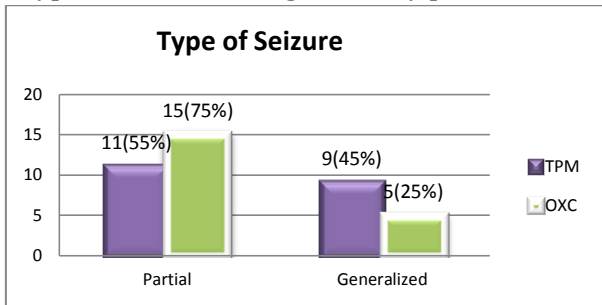
The figure shows that in TPM group male were 8(40%) and female were 12 (60%). In OXC group male were 9(45%) and female were 11(5%).

Figure-A.2: Educational status among the study patients.



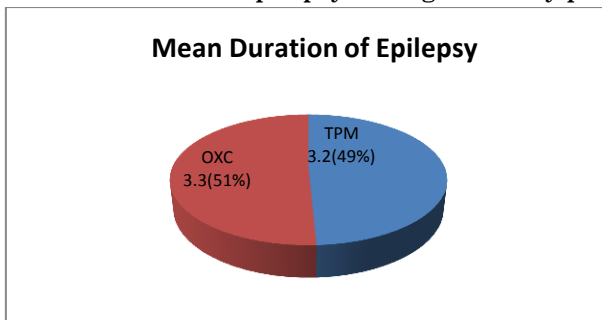
In this figure the both TPM and OXC group 7(35%) patients were in primary level and 13(65%) patients were in high school level.

Figure-A.3: Type of seizure among the study patients.



The table shows that in TPM group partial seizure patients were 11(55%) and generalized 9(45%). In OXC group partial seizure patients were 15(65%) and generalized 5(25%).

Figure-A.4: Mean duration of epilepsy among the study patients.



The figure shows that the mean duration of epilepsy patients in TPM group were 3.2(51%) and OXC group were 3.3(49%).

B) Neuropsychological outcome of the patients

Table-B.1: Neuropsychological outcome

Measures	Test Session	TPM (n=20) Mean (SD)	OXC (n=20) Mean (SD)	Significance*
Newly Diagnosed Epilepsy	Baseline	1.6(0.3-8)	1.8(0.3-8)	NS
	At 6 months	0.3(0-3)	0.5(0-8)	NS
Abnormality of EEG	Baseline (%)	12(60%)	50(10%)	NS
	At 6 months	4(20%) [§]	4(20%) [‡]	NS

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	months(%)			
List learning outcome	Baseline	56.1(9.9)	57.0(8.5)	NS [†]
	At 6 months	56.8(7.6)	59.4(8.7) [‡]	NS
Immediate Word Recall Outcome	Baseline	10.4(1.9)	10.6(1.7)	NS
	At 6 months	10.5(1.6)	11.1(1.1)	NS
Delayed Word Recall Outcome	Baseline	10.4(1.9)	10.5(1.9)	NS
	At 6 months	10.2(1.7)	11.1(1.1) [‡]	P<0.05
Word Recognition Outcome	Baseline	12.0(0.2)	11.9(0.3)	NS
	Mean (SD)			
Visual Recognition Outcome	Baseline	7.8(1.9)	7.7(2.5)	NS
	At 6 months	7.6(2.2)	7.9(2.1)	NS
Digit Span Forward Outcome	Baseline	8.0(2.4)	8.2(2.4)	NS
	At 6 months	7.0(2.8) [§]	8.1(2.4)	NS
Digit Span Backward Outcome	Baseline	6.5(2.1)	6.7(2.6)	NS
	At 6 months	6.7(2.6) [§]	7.0(2.3)	P<0.01
Verbal Fluency Outcome	Baseline	15.7(3.9)	15.6(4.4)	NS
	Mean (SD)			
	At 6 months	15.6(4.3) [§]	16.8(5.6)	P<0.05

TPM; topiramate, OXC; oxcarbazepine

*t tests for independent samples (two-sided), [†] Non-significant, P>0.05, [‡] P<0.05,[§] P<0.01, paired t test for comparison with baseline. Higher scores indicate better performance.

DISCUSSION

This was the comparative study between TPM and OXC demonstrating the cognitive dysfunctions of TPM (1-9 mg/kg/day) in epileptic patients. After 6 months of treatment, the TPM group showed a significant difference in the performance on delayed recall, backward digit span, and verbal fluency compared with the OXC group. The incidence of cognitive complaints was higher in the TPM group than in the OXC group. TPM monotherapy had negative effects on attention/concentration and verbal fluency, although it reduced monthly seizure rate and EEG abnormalities to be related to the cognitive impairment. Cognitive dysfunction was trivial with patients taking 1-9 mg/kg/day TPM. On the other hand,

OXC has a positive effect on cognition such as list learning, delayed word recall, and TMT parts A and B.

CONCLUSION

The OXC group in our study showed better performances on attention and memory tests and less cognitive complaints than did the TPM group. TPM has a negative effect on short-term memory and verbal fluency compared with OXC, an effect that could compromise occupational functioning or academic achievement

Further studies are needed to clarify the optimal daily dosage of TPM for maximizing treatment effectiveness and improving the patient's quality of life, especially in newly diagnosed epilepsy.

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