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Effect of Oxcarbazepine on Language Function in Patients With Newly Diagnosed Pediatric Epilepsy

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Background and Purpose This study aimed to determine the effects of oxcarbazepine (OXC) on the language function of patients with pediatric epilepsy.

Methods We assessed the language abilities of patients aged 5–17 years with newly diagnosed focal epilepsy and the same number of age-matched healthy children using the Test of Problem Solving (TOPS) and the Receptive and Expressive Vocabulary Test–Receptive (REVT-R). The Mean Length of Utterance–words (MLU-w) was used to estimate linguistic productivity before and after OXC initiation. All patients received OXC monotherapy with a starting dosage of 10 mg/kg/day for 1 week, which in some cases was increased to 30 mg/kg/day (or 1,200 mg/day).

Results The study finally included 41 pediatric patients (22 males and 19 females; age 9.9±3.0 years, mean±standard deviation). All language parameters of the TOPS improved significantly after initiating OXC (determining cause, 12.5±4.8–13.7±4.1 [p=0.016]; making inference, 15.6±5.6–17.4±6.4 [p<0.001]; and predicting, 9.8±5.0–11.6±4.5 [p=0.001]). However, patients who received OXC did not exhibit a significantly extended MLU-w (determining cause, p=0.493; making inference, p=0.386; and predicting, p=0.341). Receptive language scores also significantly increased after taking OXC (REVT-R: 121.0±43.1–129.4±43.8, p=0.002), but the percentage of development age to chronological age did not vary (REVT-developmental quotient: p=0.075).

Conclusions Our results suggest that OXC is safe and preserves language function in patients with pediatric epilepsy.

Keywords antiepileptic drug; epilepsy; language; oxcarbazepin.

INTRODUCTION

Epilepsy and the consequent use of antiseizure medications (ASMs) in childhood can seriously affect pediatric cognitive functions, including language development.[1,2] Traditional ASMs such as phenobarbital, benzodiazepines, and carbamazepine reportedly have negative effects on language and speech development.[3-6] These complications with using traditional ASMs lead to poor compliance and delayed drug use in patients with epilepsy, thereby disrupting the antiepileptic treatment. It is therefore essential to accurately identify the adverse neuropsychiatric, language, and cognitive effects of each ASM and to explain them to the caregivers of the patients, especially in pediatric patients.

With the establishment of the Anticonvulsant Screening Program in 1975, a new generation of ASMs that includes vigabatrin, oxcarbazepine (OXC), lamotrigine, levetiracetam, and topiramate was introduced to minimize the adverse effects from the traditional drugs.[7] However, pediatric patients may have more-unpredictable adverse effects or treatment responses than adult patients even with the new-generation drugs.[8] Among these, topiramate

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is known for its reversible yet negative effects on both cognition and language in pediatric patients, especially on verbal fluency and paragraph memory recall.[9,10] Although these effects only appear while taking the drug, they can affect learning ability, information processing, and executive function.[11,12] It is therefore also necessary to closely monitor the effects of other new-generation drugs on the cognitive and language abilities of pediatric patients.

OXC was first used medically in 1990.[13] It is a widely prescribed drug used primarily in focal seizure treatment for adults and children. Patients with various seizure types treated using OXC have presented good treatment responses with fewer side effects than those treated using traditional ASMs.[14,15] OXC also did not have significant neuropsychological and cognitive side effects compared with the chemically keto-homolog of carbamazepine.[16-18] The association between OXC and cognition has been evaluated by multiple studies that used various screening tools, including electroencephalography, story recall, and the Stroop Color and Word Test.[19-21] However, these are only approximate indicators of cognitive ability and cannot precisely assess the verbal ability of a particular child. The correlation between language and cognition has been widely debated. Although the traditional dominant view is that cognition is the main driving force of language acquisition, some scholars suggest that language is separable from cognition.[22,23] Children with epilepsy may have various language problems due to the disease itself, and this linguistic damage may be exaggerated by exposure to ASMs during their development. However, there has been little research on the relationship between language ability and OXC.[24,25]

We hypothesized that OXC has no adverse effects on language and cognitive abilities. This study aimed to determine the effects of OXC monotherapy on the language abilities of patients with newly diagnosed pediatric epilepsy, with a primary focus on discourse and pragmatic functions.

METHODS

Participants

The data of children and adolescents aged between 5 and 17 years with newly diagnosed focal epilepsy were collected retrospectively from the Hospital between 2011 to 2019. Those who had never received ASMs were diagnosed according to the International League Against Epilepsy classification from 2021 and were treated using OXC monotherapy.[26] The language tests were performed before and after OXC titration. After the start of OXC treatment, children with seizure deterioration or the requirement of drugs other than OXC were excluded from the experiment to remove the bias on language ability caused by seizure aggravation. Patients with abnormal brain magnetic resonance imaging (MRI) scans before OXC treatment and those aged ≥18 years before the follow-up test were also excluded.

For comparative analysis, the same number of age-matched school-age healthy children as in the patient group were recruited to serve as a control group. They lived in the same city, primarily visited the hospital for headaches (not migraine or tension-type headache) without other neurological symptoms, and had no history of a disease or medication use that may have affected their language development or cognitive function (e.g., intellectual disability or school failure). They had complained of mild headaches that did not require outpatient follow-up or preventive drugs, so a second language test was not required. The institutional review board of our center approved the research proposal (IRB No. 2022-02-024-003).

Methods

OXC therapy was initiated at a dosage of 10 mg/kg/day for the first week, then increased to 20 mg/kg/day for the next 2 weeks, and slowly increased thereafter at weekly intervals as needed up to 30 mg/kg/day or 1,200 mg/day.

Standard language tests were used as outcome measures to evaluate the experimental group before OXC treatment and after OXC titration. Language tests after treatment initiation were performed within 6 months to minimize the effects of improvements due to development.

Language tests

We used two types of standard language test to evaluate language abilities: 1) the Test of Problem Solving (TOPS) and 2) vocabulary tests (Receptive and Expressive Vocabulary Test–Receptive [REVT-R] and Receptive Language Vocabulary Test–Developmental Quotient [REVT-DQ]).

TOPS measures metalinguistic skills of transforming logical thinking to language in school-aged children. The illustrations used in this study were developed by the Seoul Community Rehabilitation Center in the Republic of Korea.[27] The present TOPS used 17 illustrated materials, which were divided into 3 categories: the first category consisted of 18 questions regarding cause determination, including interrogative "Why" questions; the second category consisted of 20 questions regarding making inferences, including "How" questions; and the third category consisted of 12 questions regarding making predictions, including answers to questions such as "How do you know?" and "What happens?" Scores of 0–2 were assigned depending on the responses for each category, with a maximum total score of 100. An answer to the question using linguistically appropriate vocabulary and grammar with appropriate and detailed information was scored 2 points, and inappropriate information, inexperienced expression, or

no response was scored 0 points. Patient responses were recorded and documented immediately after test completion. Scores were divided into raw, mean, and total scores for each category. The length of articulation for each answer was compared using the Mean Length of Utterance–words (MLU-w), which defines a mean score of the length of articulation obtained by adding all of the words in the answer and dividing by the number of sentences in the answer.[28]

REVT has been approved for the evaluation of receptive and expressive vocabulary development skills and is applicable to both children (from ≥2 years) and adults (>18 years).[29] It consists of 185 items (98 nouns, 68 verbs, and 19 adjectives and adverbs), and the target vocabulary is derived using pictures. Raw scores were calculated based on baseline and ceiling results, and they provide the vocabulary development age of the subject. REVT-DQ was measured by dividing the development age by the chronological age and multiplying by 100.

Statistical analysis

Statistical analysis was performed using SPSS (version 23.0, IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was performed to determine variable normality. Independent *t*-tests were used to compare differences between the control and patient groups for the variables that satisfied the normality assumption, while Mann-Whitney tests were conducted for the other variables. Paired *t*-tests and Wilcoxon signed-rank tests were used to compare differences between before and after OXC initiation. Scores are presented as mean±standard-deviation values, and significance was indicated by $p \leq 0.05$.

RESULTS

Patient characteristics

We included 59 patients with newly diagnosed epilepsy who underwent OXC monotherapy during the study period. The excluded patients comprised five with lesions on brain MRI distinct enough to affect language abilities, four who required additional use of other ASMs due to recurrent seizure or side effects, and nine who did not receive a second examination within 6 months. Finally, 41 children with epilepsy (22 males and 19 females; age=9.9±3.0 years) who received OXC monotherapy (mean dosage=25.0 mg/kg/day) (Table 1) were analyzed. The study included 17 patients with self-limited epilepsy with centrotemporal spikes, 16 with frontal lobe epilepsy, 5 with temporal lobe epilepsy, 2 with childhood occipital visual epilepsy, and 1 with idiopathic generalized epilepsy (Table 1). Although they did not undergo cognitive tests, three children had a language development index of 2 standard deviations or less on the REVT, and the rest were within the normal range of language development. None of them experienced seizure recurrence before the follow-up language test. The age of the control group (comprising 19 males and 22 females) was 10.2±2.5 years. Follow-ups were performed after 45–201 days, with an average time from the first to the second evaluation of 105±37.9 days (Table 1).

Table 1. Demographic characteristics of the patient and control groups

	n	
Patient group	41	
Sex (male:female)		22:19
Age (yr)		9.9±3.0 (70 to 166 months)
Dosage of OXC		25 mg/kg/d (max 1,200 mg/d)
Term of test (days)		105.4±37.9 (45 to 201)
Seizure type		
SeLECTS	17	
FLE	16	
TLE	5	
COVE	2	
IGE	1	
REVT-DQ		
DQ<-2 SD	3	
-2 SD≤DQ<-1 SD	2	
-1 SD≤score<0	16	
Score≥0	20	
Control group		
Sex (male:female)		19:22
Age (yr)		10.2±2.5

COVE, childhood occipital visual epilepsy; FLE, frontal lobe epilepsy; IGE, idiopathic generalized epilepsy; OXC, oxcarbazepine; REVT-DQ, Receptive Language Vocabulary Test-Developmental Quotient; SD, standard deviation; SeLECTS, self-limited epilepsy with centrotemporal spikes; TLE, temporal lobe epilepsy.

Comparison of TOPS scores

Fig. 1 compares the average differences between the control and patient groups in the determining-cause, making-inference, and predicting scores of TOPS. The control group had significantly higher TOPS scores than the patient group before taking OXC (pre-OXC) in determining cause ($p<0.001$), making inference ($p=0.008$), predicting ($p<0.001$), and in the total score ($p<0.001$) (Fig. 1). We further found that the scores of patients more closely approached the scores of healthy children after OXC initiation (on-OXC) in all categories. However, there were also significant differences between the scores of on-OXC patients and the control group (determining cause, $p=0.016$; making inference, $p<0.001$; predicting, $p=0.001$; total score, $p<0.001$).

The highest score in the determining-cause category was 24. The pre-OXC patients obtained a score of 12.5±4.8, which increased significantly to 13.7±4.1 in on-OXC patients ($p=0.016$) (Fig. 1).

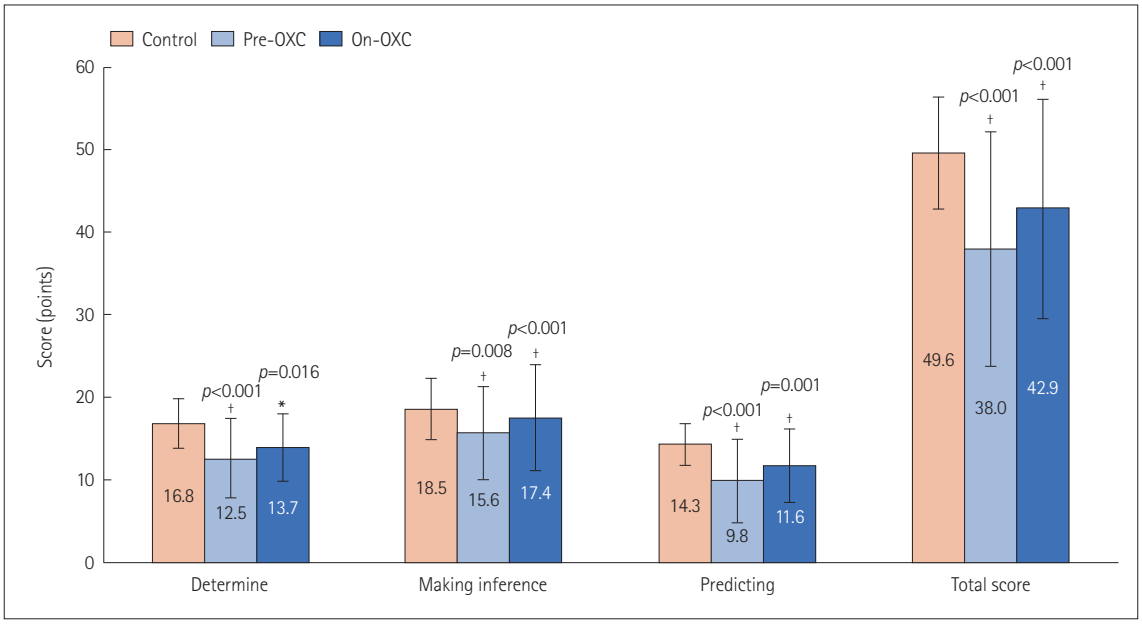

Fig. 1. Comparison of the scores for the Test of Problem Solving. The values on the pre-OXC graph are the *p* values obtained in comparisons of the control and pre-OXC groups, and the values on the OXC graph are the results of this comparison. The scores in the control group (healthy children) were significantly higher in all categories than those in the patient groups (determining cause, p=0.001; making inference, p=0.008; predicting, p<0.001; total score, p<0.001). Likewise, the scores for on-OXC were higher than those for pre-OXC (determining cause, p=0.016; making inference, p<0.001; predicting, p=0.001; total score, p<0.001). *p<0.05; †p<0.01. On-OXC, after OXC initiation; OXC, oxcarbazepine; Pre-OXC, before OXC medication.

The highest score for the making-inference category was 29. The scores for patients with pediatric epilepsy changed from 15.6±5.6 pre-OXC to 17.4±6.4 on-OXC (p<0.001) (Fig. 1). Upon examining verbal expression in the making-inference category, on-OXC patients expressed various methods of problem-solving based on their experience, and were sometimes confident in their answers.

The highest score in the predicting category was 19, and we observed a significant difference between the mean pre-OXC and on-OXC scores for patients with pediatric epilepsy (9.8±5.0 and 11.6±4.5, respectively, p=0.001) (Fig. 1). Regarding problem-solving methods and verbal expression of answers, there were significant differences between the pre-OXC and on-OXC groups.

Out of the maximum score of 100, the score for pre-OXC was 38.0±14.2, which increased significantly to 42.9±13.3 on-OXC (p<0.001) (Fig. 1). Six patients (14.6%) had a lower score on-OXC than pre-OXC, with differences of -7 to -2 points (Fig. 2). There was no difference in those scores of 4 patients (9.8%), and the scores of the remaining 31 patients (75.6%) had improved by 1 to 14 points from their on-OXC scores. The score in the control group was 49.6±6.8, which was significantly higher than that for pre-OXC and on-OXC in the patient group (pre-OXC, p<0.001; on-OXC, p=0.006).

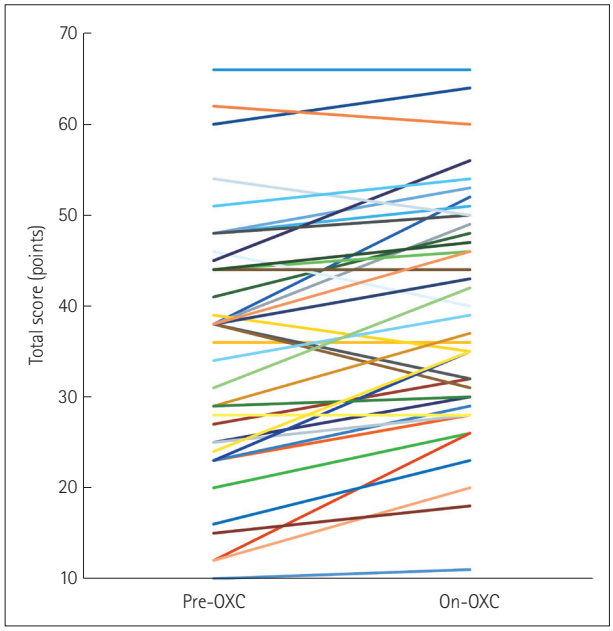

Fig. 2. Changes between before and after OXC medication in the total Test of Problem Solving scores in the patient groups. Of the 41 patients, 31 (75.6%) had improved scores and 6 had reduced scores. On average the total scores increased significantly (p<0.001). On-OXC, after OXC initiation; OXC, oxcarbazepine; Pre-OXC, before OXC medication.

MLU-w in TOPS

Unlike in TOPS, MLU-w scores did not differ significantly between the control and pre-OXC groups in the determining-cause and making-inference categories, while there were significant differences among the predicting and total-score categories (predicting, p=0.001; total score, p=0.015) (Table 2).

Table 2. Comparison of scores for the Mean Length of Utterance in words for problem-solving

	Mean±SD (words)	*t*	*p*
Comparison between pre-OXC and control group			
Determine cause		-1.675	0.094
Pre-OXC	5.0±1.7		
Control	5.4±1.5		
Making inferences		-1.846	0.065
Pre-OXC	5.0±2.1		
Control	5.5±1.6		
Predicting		-3.730	0.001†
Pre-OXC	4.8±2.2		
Control	5.6±1.6		
Total score		-2.444	0.015*
Pre-OXC	4.9±1.8		
Control	5.4±1.5		
Comparison between pre-OXC and on-OXC group			
Determine cause		-0.686	0.493
Pre-OXC	5.0±1.7		
On-OXC	5.2±1.3		
Making inferences		-0.867	0.386
Pre-OXC	5.0±2.1		
On-OXC	5.4±1.9		
Predicting		-0.953	0.341
Pre-OXC	4.8±2.2		
On-OXC	5.2±1.8		
Total score		-1.030	0.303
Pre-OXC	4.9±1.8		
On-OXC	5.3±1.6		

*p<0.05; †p<0.01. On-OXC, after OXC initiation; OXC, oxcarbazepine; Pre-OXC, before OXC medication; SD, standard deviation.

In the determining-cause category, the MLU-w score increased on-OXC from 5.0±1.7 to 5.2±1.3, but the difference was not significant (p=0.493) (Table 2). Regarding making inference and predicting, MLU-w scores on-OXC increased from 5.0±2.1 to 5.4±1.9 and from 4.8±2.2 to 5.2±1.8, respectively, but no significant difference was observed (p=0.386 and p=0.341, respectively) (Table 2). The total problem-solving MLU-w score changed from 4.9±1.8 to 5.3±1.6 on-OXC (p=0.303) (Table 2).

Comparison of REVT scores

The REVT score represented the development ages of the children. Similarly, the control group achieved significantly higher scores for both REVT-R and REVT-DQ compared with patient groups (REVT-R, p=0.021; REVT-DQ, p=0.001) (Table 3). The development age for patients with pediatric epilepsy according to REVT pre-OXC and on-OXC changed significant from 10.1±3.6 to 10.8±3.7 years (p=0.002) (Table 3).

Table 3. Results of the REVT-R

	Mean±SD	*t*	*p*
Comparison between pre-OXC and control group			
REVT-R (yr)		-2.301	0.021*
Pre-OXC	10.1±3.6		
Control	11.2±3.4		
REVT-DQ (%)		-3.572	0.001†
Pre-OXC	94.4±16.9		
Control	108.6±18.9		
Comparison between pre-OXC and on-OXC group			
REVT-R (yr)		-3.051†	0.002†
Pre-OXC	10.1±3.6		
On-OXC	10.8±3.7		
REVT-DQ (%)		-1.830	0.075
Pre-OXC	94.4±16.9		
On-OXC	97.1±18.6		

*p<0.05; †p<0.01. On-OXC, after OXC initiation; OXC, oxcarbazepine; Pre-OXC, before OXC medication; REVT-DQ, Receptive Language Vocabulary Test-Developmental Quotient; REVT-R, Receptive and Expressive Vocabulary Test; SD, standard deviation.

However, the REVT-DQ score adjusted for chronological age changed from 94.4%±16.9% to 97.1%±18.6%, without a significant difference (p=0.075) (Table 3).

DISCUSSION

This study investigated the effect of OXC with a focus on linguistic characteristics in patients with pediatric epilepsy. We analyzed the influence of OXC medication on language development using TOPS and REVT-R scores. We utilized TOPS to compare the problem-solving abilities of the examinees, which refers to their ability to comprehend the causes of events, speculate on conditions, and solve problems. All three categories (determining-cause), making-inference, and predicting) showed significant differences in problem-solving skills pre-OXC and on-OXC medication, with the scores increasing after OXC monotherapy (Fig. 1). This indicates that OXC may help to promote language-related problem-solving skills.

MLU-w is the most widely used tool for measuring expressive linguistic proficiency in clinical and language research of children.[30,31] Comparisons of MLU-w scores indicated improvements in all three categories and in the total scores, but the difference between pre-OXC and on-OXC was not significant (Table 2). REVT-R was used to analyze receptive vocabulary development skills, which are the abilities to see, hear, and understand linguistic stimuli and tended to improve in overall scores, but there was no difference in REVT-DQ when also considering chronological age (Table 3). The results suggest that patients taking OXC experience no definite adverse ef-

fects on problem-solving abilities without compromising linguistic productivity and receptive vocabulary development skills.

Continuously controlling seizures is the most important aim of antiepileptic treatment.[32] However, the adverse effect of anticonvulsants on cognitive and linguistic capabilities must be considered when treating pediatric patients with epilepsy because any impairment in language function during childhood and adolescence may affect the quality of life in adulthood, leading to substantial difficulties in social adaptation.[33,34]

The few studies that analyzed language development after OXC treatment found positive effects, including cognitive function preservation. However, most of these studies were limited to a small number of adult patients.[35-38] Conversely, studies that included pediatric patients found that OXC had no negative influence on cognitive function,[7,39] and there is a lack of evidence regarding the effects of OXC on linguistic ability. The present study successfully established that OXC treatment does not promote any remarkable adverse effects but rather enhances the pragmatic and discourse aspects, which are crucial in language use.

On the basis of these findings, we can infer that OXC medication should be prescribed to patients with pediatric epilepsy without concern about possible linguistic problems. Eun et al.[39] drew similar conclusions, asserting that OXC is an effective anticonvulsant for both adults and children and is safe to use without inducing verbal or cognitive adverse effects.

The limitations of this study include its small sample. Furthermore, we could not carry out long-term monitoring of the study participants. An animal study performed in 2009 found that exposing the developing brain to phenobarbital, clonazepam, valproic acid, carbamazepine, or topiramate inhibits neurogenesis of the dorsal hippocampus.[40] This implicated potential negative effects from long-term exposure to ASMs on the developing brains of children. It is therefore important to consider the consequences of long-term use or discontinuation of a medicine after treatment completion. An MLU-w analysis based on the TOPS was also performed. However, this analysis alone could not explain qualitative points, such as mistakes during the study course, because it deals with quantitative results.

In conclusion, this study has provided substantial evidence that physicians can safely prescribe OXC to children with epilepsy without potential adverse effects on their language-producing abilities.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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None

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