Benign Childhood Epilepsy with Centrotemporal Spikes: To Treat or Not to Treat

Soonhak Kwon[1], Tae Gyu Hwang[2], Junhwa Lee[3], Doo-Kwun Kim[4], Hye-Eun Seo[1]

[1]Department of Pediatrics, Kyungpook National University Hospital, Kyungpook National University School of Medicine, Daegu; [2]Department of Pediatrics, Inje University Haeundae Paik Hospital, Busan; [3]Department of Pediatrics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon; [4]Department of Pediatrics, Dongguk University College of Medicine, Gyeongju, Korea

Background and Purpose: The aim of this study was to evaluate the benefits and risks of oxcarbazepine (OXC) monotherapy in children with newly diagnosed, benign partial epilepsy based on clinico-electrical and neuropsychological evaluation over time.

Methods: The study was open label, prospective, multicenter based. A total of 39 children with BRE were involved in the study. They were randomized into two groups (T; treatment with OXC, NT; No treatment) to compare the effectiveness of OXC treatment. All children underwent EEGs with quantification and a comprehensive battery of neuropsychological tests at the first visit and follow up visit at 6 months.

Results: The subjects made a slight progress in general intelligence measures over time in both groups (95.4±10.5 to 97.6±7.5 for T, 107.6±17.3 to 111.4±18.6 for NT). Memory and frontal executive functions did not change over time in both groups in terms of the memory quotient (MQ) (106.7±27.5 to 103.4±19.3 for T, 105.8±13.2 to 104.9±17.2 for NT) and executive intelligence quotient (EIQ) (114.7±18.3 to 108.9±12.5 for T, 100.6±25.1 to 101.2±13.9 for NT). However, when sub-domain scores were compared between the two groups, the treatment group got significantly worse over time in the verbal fluency test (11.5±3.8 to 8.0±1.4 for T, 10.3±3.9 to 11.5±2.1 for NT; $p<0.05$) and level 1 of Stroop test (9.3±3.0 to 7.5±1.3 for T, 11.0±3.7 to 11.2±2.6 for NT; $p<0.05$). The subjects might have cognitive and behavioral difficulties in association with frontal lobe dysfunctions, but these difficulties did not seem to be dependent on the number of seizures, the abundance of subclinical epileptiform discharges, or the anti-epileptic treatment.

Conclusions: We think that OXC monotherapy is effective for children with BRE, but is to be given to the selected patients such as patients with prolonged or frequent seizures. However, further studies are needed to have a better understanding in this matter. **(2013;3:1-6)**

Key words: Child, Epilepsies, Partial, Cognition Disorders, Behavior, Neuropsychological tests

Introduction

Benign childhood epilepsy with centrotemporal spikes (BECTS) or benign rolandic epilepsy (BRE) is the most common epilepsy syndrome in children and is age related and genetically determined. Children with BECTS usually exhibit normal development and normal intelligence. However, several recent studies have reported a higher risk of cognitive, behavioral and other difficulties in association with frontal lobe dysfunctions in these children,[1-9] although the exact profile of these difficulties are not yet clear. Furthermore, the amount of subclinical epileptiform discharges tends to increase during sleep. A meta-analysis by Nicolai and Aldenkamp examined the effects of subclinical localized epileptiform discharges during sleep in children with BCECTS on cognition and behavior. It remains to be shown whether antiepileptic drug (AED) treatment of nocturnal discharges in these children improves cognitive and behavioral problems.[10]

In this study, the benefits and risks of oxcarbazepine (OXC) monotherapy as a first-line AED in children with newly diagnosed BCECT were evaluated based on clinico-electrical and neuropsychological findings over time.

Materials and Methods

Subjects

Children aged 5-15 years of age were eligible for this study when they experienced two or more seizures over the past 6 months and had been diagnosed with BECTS by pediatric neurologists. All subjects developed normally and their performance in school was within the normal range at the baseline. Exclusion criteria included primarily generalized seizures, partial epilepsies of a symptomatic etiology, neurodegenerative conditions, a history of psychiatric conditions and a history of taking antiepileptic drugs over the previous three months. They were recruited from four tertiary medical centers that function as major referral centers in four different regions of South Korea.

Study design

The study was a multicenter based, randomized, open label, prospective clinical trial of treatment/non-treatment comparison design. The study consisted of screening, randomization and a 30 week treatment phase. Each center was given a separate and independent randomization protocol using a random code assignment. The subjects were randomized into two groups (T; treatment with OXC, NT; No treatment) to compare the effectiveness of OXC treatment. In the treatment group, OXC was initially given once a day or twice a day at a dose of 5-10 mg/kg/day and titrated to 10-20 mg/kg/day over a week. This regiment allowed one to increase the dose to a therapeutic range if the subjects had increased frequency or severity of

Figure 1. Study design. The subjects were randomized into two groups (treatment with OXC, No treatment) to compare the effectiveness of OXC treatment. In the treatment group, OXC was given once a day or twice a day at the same dose. All children underwent sleep EEGs and comprehensive neuropsychological tests at the first and 6 month follow up visits.

seizures in comparison with those of the baseline. All children underwent EEGs with quantification and a comprehensive batter of neuropsychological tests at the first and 6 month follow up visits (Fig. 1).
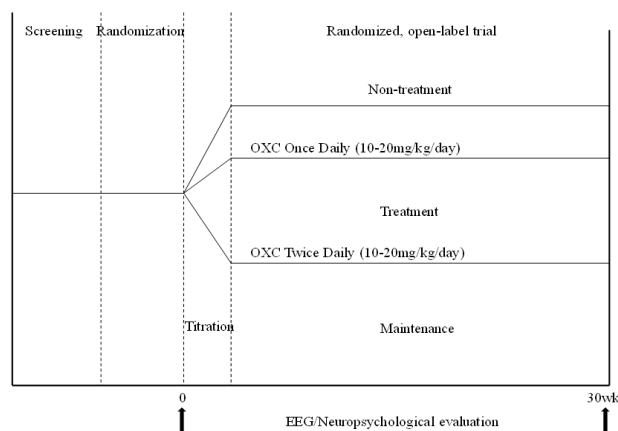
Outcome measures, statistical methods and others

The primary outcome parameter was changes in cognition, attention, and behavior in the neuropsychological tests due to medical treatment over time. The secondary parameter included seizure control rate, normalization or improvement of EEG and comparative efficacy of OXC daily or twice a day treatments during the study period. The EEGs were read by two or more experienced specialists. The location and frequency of spikes were quantified for each subject. The spike index was calculated by dividing the total number of spikes by the total time the subject was evaluated.

The subjects went through a comprehensive battery of neuropsychological tests to evaluate various aspects of mental function, including cognition, attention, memory, executive function, behavior and emotion, etc. The tests are shown in Table 1.

The data were statistically analyzed using PASW Statistics 18.0.0 (IBM Corporation, NY, USA). Statistical analysis of the test results was performed using means and their corresponding standard deviations (SD). Significant correlations among independent scores regarding the effects of medical treatment were evaluated using a student t-test or two way repeated measures ANOVA. Statistical significance was regarded at p-value <0.05.

The study was formally approved by the Institutional Review Board (74005-1379).

Results

Out of 39 children with BECTS, 29 (13 for T and 16 for NT) completed the study. Ten children were dropped due to the failure of follow-up evaluation (3 for T) and loss of follow-up (7 for NT). The mean ages of the subjects were 8.2±2.3 years for the treatment group and 8.5±2.3 years for the non-treatment group. At the time of baseline,

Table 1. Neuropsychological Tests used in this study

Korean versions of Wechsler Intelligence Scale for Children III
Frontal Executive Neuropsychological Test (K-FENT)
Auditory Verbal Learning Test (AVLT)/Rey Complex Figure Test (RCFT)
Wisconsin card Sorting Test (WCST)
Attention Deficit Diagnostic Scale, Visual (K-ADS)
Child Behavior Checklist (K-CBCL)

the average monthly seizure frequencies of the subjects were 0.8± 0.7 for the treatment group and 0.9±1.0 for the non-treatment group. The average spike index (frequency/min) was 17.4±19.8 on the left side and 15.5±17.6 on the right in the treatment group and 13.9±22.5 on the left side and 7.2±16.2 on the right of the non-treatment group (Table 2).

Table 3 presents results on the clinical and neuropsychological assessment of the subjects over time. 54% of OXC treatment group remained seizure free and 23% showed an average monthly reduction in seizure frequency of more than 50% during the first 6 month as did 50% and 19% of the non-treatment group. Statistically there was no significant difference between the two groups. The sleep EEGs became normalized in 15% of the treatment group and 19% of the non-treatment group after six months of treatment. As for the spike index, it increased by 20-50% in the treatment group after 6 months of treatment and fell by 20-90% in the non-treatment group over the same time period (p>0.05). Furthermore, the spike index of the right hemisphere decreased more in the non-treatment group

than in the treatment group; however this different was not statistically significant (7.2±16.2 to 3.8±7.9 in NT vs. 15.5±17.6 to 19.1± 18.4 in T). The subjects made slight progress in general intelligence measures over time in both groups. Surprisingly, the treatment group had a higher performance intelligence quotient (PIQ), which was not significant (95.3±11.6 to 103.9±6.3 in T vs. 103.4±17.1 to 110.4±17.9 in NT).

As summarized in Table 4, overall memory and frontal executive functions did not change over time in both groups in terms of the

Table 2. Demographic and clinical features of the subjects (n=29)

	Treatment (n=13)	Non-treatment (n=16)
Male/Female	6/7	11/8
Age (yr)	8.2±2.3	8.5±2.3
Average monthly seizure frequency	0.8±0.7	0.9±1.0
Spike index (frequency/min)		
Left	17.4±19.8	13.9±22.5
Right	15.5±17.6	7.2±16.2

Table 3. Clinical and neuropsychological findings of the subjects over time (n=29)

	Treatment (n=13)		Non-treatment (n=16)		p-value
	Baseline	6 mon	Baseline	6 mon	
Seizure frequency	0.8±0.7	0.5±0.8	0.9±1.0	0.5±2.0	NS
Seizure freedom		7 (54%)		8 (50%)	NS
Reduction > 50%		3 (23%)		3 (19%)	NS
Spike index					
Left	17.4±19.8	26.2±18.0	13.9±22.5	11.8±20.0	NS
Right	15.5±17.6	19.1±18.4	7.2±16.2	3.8±7.9	NS
EEG (-)[*]		2 (15%)		3 (19%)	NS
FIQ	95.4±10.5	97.6±7.5	107.6±17.3	111.4±18.6	NS
VIQ	100.5±11.1	91.9±8.8	109.6±16.3	110.4±18.3	NS
PIQ	95.3±11.6	103.9±6.3	103.4±17.1	110.4±17.9	NS

P-values based on two way repeated measures, ANOVA.
Seizure frequency, Average seizure frequency/month; Spike index, frequency/minute; FIQ, Full-scale intelligence quotient; VIQ, Verbal intelligence quotient; PIQ, Performance intelligence quotient; NS, Not significant statistically.
[*]EEG (-), normalization of sleep EEG.

Table 4. Results of frontal executive functions and memory over time (n=29)

	Treatment (n=13)		Non-treatment (n=16)		p-value
	Baseline	6 mon	Baseline	6 mon	
EIQ	114.7±18.3	108.9±12.5	100.6±25.1	101.2±13.9	NS
MQ	106.7±27.5	103.4±19.3	105.8±13.3	104.9±17.2	NS
WCST	50.8±11.0	62.3±14.2[*]	60.3±14.3	67.8±22.3	p<0.05

p-values based on two way repeated measures, ANOVA.
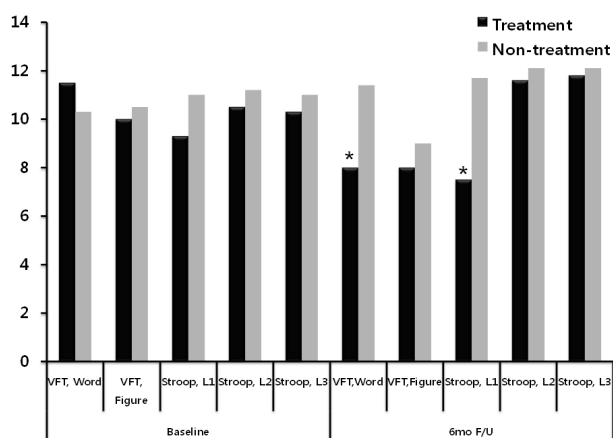EIQ, Executive Intelligence quotient; MQ, Memory quotient; WCST, Wisconsin card sorting test.
[*]p<0.05.

memory quotient (MQ) (106.7±27.5 to 103.4±19.3 in T vs 105.8± 13.2 to 104.9±17.2 in NT) and executive intelligence quotient (EIQ) (114.7±18.3 to 108.9±12.5 in T vs. 100.6±25.1 to 101.2±13.9 in NT). However, when sub-domain scores were compared between the two groups, the treatment group got significantly worse over time in the verbal fluency test (11.5±3.8 to 8.0±1.4 in T vs. 10.3±3.9 to 11.5±2.1 in NT; $p<0.05$) and level 1 of Stroop test (9.3±3.0 to 7.5±1.3 in T vs. 11.0±3.7 to 11.2±2.6 in NT; $p<0.05$) (Fig. 2). In contrast, the treatment group had better "frontal" lobe functions in the Wisconsin card sorting test (WCST) over time than the non-treatment group (50.8±11.0 to 62.3±14.2 in T vs. 60.3±14.3

Figure 2. Verbal fluency and Stroop tests between treatment and non-treatment groups. The scores for the word and verbal fluency and level 1 Stroop tests for the treatment group got significantly got worse over time when compared with the non-treatment group.

to 67.8±22.3 in NT; $p<0.05$). Otherwise, no significant differences were observed in the sub-domains of the Auditory Verbal Learning Test (AVLT)/Rey Complex Figure Test (RCFT) and Frontal Executive Neuropsychological Test (K-FENT) between the two groups.

In the computerized attention measurements (Attention Deficit Diagnostic Scale, Visual; K-ADS), which is vision based, the non-treatment group appeared more inattentive and impulsive and the treatment group scored higher on the sub-domains; however, this difference was not statistically significant (54.0±8.2 to 62.3±14.2 in T vs. 60.3±14.3 to 67.8±22.3 in NT for inattentiveness and 50.8± 11.0 to 62.3±14.2 in T vs. 60.3±14.3 to 67.8±22.3 in NT for impulsivity, $p>0.05$). In addition, there were no significant differences in the sub-items of Child Behavior Checklist (K-CBCL) overtime in both groups. As shown in Table 5, no differences in seizures and neurocognitive functions were observed for the group receiving OXC treatment twice a day, but rather this treatment appeared to aggravate behavior, especially aggression on K-CBCL (38.0±11.5 to 31.0±11.3 in once daily treatment group and 46.4±11.6 to 50.8±15.58, $p<0.05$).

Discussion

Recent studies have demonstrated that BECTS may present with cognitive, behavioral and other difficulties in association with frontal lobe dysfunctions[1-9,11,12] and subclinical localized epileptiform discharges during sleep may affect or worsen their cognition and behaviors.[10] However, whether or not children with BECTS need anti-

Table 5. Comparison between OXC treatment once daily and twice daily over time (n=13)

	Once daily (n=4)		Twice daily (n=9)		p-value
	Baseline	6 mon	Baseline	6 mon	
Seizure frequency	0.4±0.4	0.4±0.6	1.0±0.8	0.8±0.7	NS
Seizure freedom		2 (50%)		5 (56%)	NS
Reduction > 50%		1 (25%)		1 (11%)*	$p>0.05$
Spike index					
Left	27.6±26.5	33.0±19.2	12.8±15.8	22.8±18.1*	$p>0.05$
Right	21.0±27.1	24.7±24.0	13.0±13.0	16.3±16.8	NS
EEG (-)[†]		0 (0%)		1 (11%)	NS
FIQ	94.8±10.8	98.0±10.0	95.8±11.0	97.4±9.1	NS
VIQ	105.3±12.5	92.0±7.1	98.1±10.4	91.8±10.1	NS
PIQ	92.5±14.7	104.5±9.2	96.8±10.6	103.6±6.1	NS
Aggression[‡]	38.0±11.5	31.0±11.3	46.4±11.6	50.8±15.58*	$p>0.05$

p values based on two way repeated measures, ANOVA.
FIQ, Full-scale intelligence quotient; VIQ, Verbal intelligence quotient; PIQ, Performance intelligence quotient; NS, Not significant statistically. *$p<0.05$. [†]EEG (-), normalization of sleep EEG. [‡]Aggression, aggression on K-CBCL.

epileptic drug treatment is still controversial. Furthermore, there have been few prospective trials in children with BECTS regarding the effects of antiepileptic drugs on cognition and behavior. In this study, the benefits and risks of oxcarbazepine (OXC) monotherapy in these children were evaluated based on clinico-electrical and neuro-psychological changes over time.

Unlike previous studies,[13-15] this trial failed to demonstrate OXC efficacy in the seizure control. There were no significant differences between treatment and non-treatment groups even though 54% of OXC treated patients were seizure free at the end of the first 6 months. However, these results likely occurred because of the small sample size, relatively short period of follow-up and wide spectrum of conditions examined.[16]

Based on the results of this study, only 15% of the treatment group and 19% of the non-treatment group showed normalization of EEG after six months. In addition, the spike rate increased in the treatment group and decreased in the non-treatment group after 6 months; however, this difference was not statistically significant. These findings are not in agreement with previous studies.[17,18] Again, this likely occurred because of the small sample size and low dose of OXC used during the study period. Despite these findings, the general intelligence measures for both groups slightly improved over time. Furthermore, the intelligence quotient (PIQ) slightly increased in the treatment group; however, this increment was not statistically significant. These results indicate that treatment with OXC might also have a positive effect on cognition, which has been observed in other studies.[8]

To the best of our knowledge, few previous studies have evaluated the frontal lobe functions in children with BCECTS in relation to medical treatment.[15] This pilot study demonstrated that overall memory and frontal executive functions did not change over time regardless of treatment. When sub-domain scores were compared between two groups, the scores for the verbal fluency ($p<0.05$) and level 1 stroop tests ($p<0.05$) got worse over time for the treatment group. In contrast, the treatment group showed better frontal lobe functions in the WCST over time than the non-treatment group ($p<0.05$). These findings were troublesome because they indicate that administration of OXC may interfere with language development in children. However, further studies are needed to conclusively demonstrate that this was the case.

A few studies have demonstrated a significant correlation between treatment and positive effects on behavioral difficulties.[10,19-21] In this study, the non-treatment group appeared more inattentive and impulsive, whereas OXC treatment appeared to produce negative effects in the vision based, computerized attention measures; however, this difference was not statistically significant when compared with the other group. In addition, both groups did not show any significant behavioral changes overtime on K-CBCL. Thus, it is still not clear whether drug treatment can improve or worsen attention and behavior.

Since seizures mostly occur at night in children with BCECTS, we tried to assess the effect of single daily dose, especially in the late evening or before going to bed. As expected, treatment with OXC twice a day did not produce a better outcome in controlling seizures and cognitive functions, but rather seemed to aggravate behavior, especially aggression. Based on these findings, it might be better to administer OXC treatment in a single dose once a day in the evening or prior to sleep. Moreover, these results partly support the effects of treating nocturnal EEG discharges on cognition and behavior reported in previous studies.[8]

This study is limited due to its small sample size, the heterogeneity of subjects, and the lack of information about the potential effects of epileptiform discharges during the neuropsychological assessment. In addition, some neuropsychological tests, such as ADS, could not be measured reliably in preschool children due to their immature grapho-motor skills. Large scaled, more objective studies are needed to elucidate these effects in children with BCECTS.

In conclusion, this study revealed that children with BCECTS have a higher chance of having cognitive and behavioral difficulties as well as frontal lobe dysfunctions, but these difficulties did not seem to be dependent on the number of seizures, the abundance of subclinical epileptiform discharges, or the anti-epileptic treatment. We therefore believe that OXC monotherapy is an effective measure for children with BRE, but should be tried to selected patients who have prolonged or frequent seizures. However, further studies are needed to elucidate this matter.

Acknowledgements

References

1. Tedrus GM, Fonseca LC, Castilho DP, Pacheco EM, Campregher AA, Bittar MC. Benign childhood epilepsy with centro-temporal spikes: evolutive clinical, cognitive and EEG aspects. *Arq Neuropsiquiatr* 2010;68:550-5.

2. Goldberg-Stern H, Gonen OM, Sadeh M, Kivity S, Shuper A, Inbar D. Neuropsychological aspects of benign childhood epilepsy with centrotemporal spikes. *Seizure* 2010;19:12-6.

3. Danielsson J, Petermann F. Cognitive deficits in children with benign rolandic epilepsy of childhood or rolandic discharges: a study of children between 4 and 7 years of age with and without seizures compared with healthy controls. *Epilepsy Behav* 2009;16:646-51.

4. Ay Y, Gokben S, Serdaroglu G, et al. Neuropsychologic impairment in children with rolandic epilepsy. *Pediatr Neurol* 2009;41:359-63.

5. Hoie B, Sommerfelt K, Waaler PE, Alsaker FD, Skeidsvoll H, Mykletun A. The combined burden of cognitive, executive function, and psychosocial problems in children with epilepsy: a population-based study. *Dev Med Child Neurol* 2008;50:530-6.

6. Duman O, Kizilay F, Fettahoglu C, Ozkaynak S, Haspolat S. Electrophysiologic and neuropsychologic evaluation of patients with centrotemporal spikes. *Int J Neurosci* 2008;118:995-1008.

7. Wirrell E, Sherman EM, Vanmastrigt R, Hamiwka L. Deterioration in cognitive function in children with benign epilepsy of childhood with central temporal spikes treated with sulthiame. *J Child Neurol* 2008; 23:14-21.

8. Baglietto MG, Battaglia FM, Nobili L, et al. Neuropsychological disorders related to interictal epileptic discharges during sleep in benign epilepsy of childhood with centrotemporal or Rolandic spikes. *Dev Med Child Neurol* 2001;43:407-12.

9. Weglage J, Demsky A, Pietsch M, Kurlemann G. Neuropsychological, intellectual, and behavioral findings in patients with centrotemporal spikes with and without seizures. *Dev Med Child Neurol* 1997;39: 646-51.

10. Nicolai J, Aldenkamp AP, Arends J, Weber JW, Vles JS. Cognitive and behavioral effects of nocturnal epileptiform discharges in children with benign childhood epilepsy with centrotemporal spikes. *Epilepsy Behav* 2006;8:56-70.

11. Billard C, Fluss J, Pinton F. Specific language impairment versus Landau-Kleffner syndrome. *Epilepsia* 2009;50 Suppl 7:21-4.

12. Lillywhite LM, Saling MM, Harvey AS, et al. Neuropsychological and functional MRI studies provide converging evidence of anterior language dysfunction in BECTS. *Epilepsia* 2009;50:2276-84.

13. Tzitiridou M, Panou T, Ramantani G, Kambas A, Spyroglou K, Panteliadis C. Oxcarbazepine monotherapy in benign childhood epilepsy with centrotemporal spikes: a clinical and cognitive evaluation. *Epilepsy Behav* 2005;7:458-67.

14. Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006;47:1094-120.

15. Donati F, Gobbi G, Campistol J, et al. Effects of oxcarbazepine on cognitive function in children and adolescents with partial seizures. *Neurology* 2006;67:679-82.

16. Lundberg S, Eeg-Olofsson O. Rolandic epilepsy: a challenge in terminology and classification. *Eur J Paediatr Neurol* 2003;7:239-41.

17. Bast T, Volp A, Wolf C, Rating D. The influence of sulthiame on EEG in children with benign childhood epilepsy with centrotemporal spikes (BECTS). *Epilepsia* 2003;44:215-20.

18. Kramer U, Shahar E, Zelnik N, et al. Carbamazepine versus sulthiame in treating benign childhood epilepsy with centrotemporal spikes. *J Child Neurol* 2002;17:914-6.

19. De Negri M, Baglietto MG, Gaggero R. Benzodiazepine (BDZ) treatment of benign childhood epilepsy with centrotemporal spikes (BECCT). *Brain Dev* 1997;19:506.

20. Deltour L, Quaglino V, Barathon M, De Broca A, Berquin P. Clinical evaluation of attentional processes in children with benign childhood epilepsy with centrotemporal spikes (BCECTS). *Epileptic Disord* 2007; 9:424-31.

21. Besag FM. Behavioral aspects of pediatric epilepsy syndromes. *Epilepsy Behav* 2004;5 Suppl 1:S3-13.