Oxcarbazepine monotherapy in children with benign epilepsy with centrotemporal spikes improves quality of life

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Abstract

Background: Benign epilepsy with centrotemporal spikes (BECTS) is the most common type of childhood idiopathic focal epilepsy. BECTS is associated with pervasive cognitive deficits and behavior problems. While seizures can be easily controlled, it is crucial to select anti-epileptic drugs that do not impair cognition, do not cause psychosocial effects, and improve the quality of life. Previous studies showed effects of oxcarbazepine (OXC) monotherapy on the cognitive and psychosocial profiles of patients with BECTS. Here, we studied the effects of OXC monotherapy on the neuropsychologic profiles and quality of life in patients with BECTS in China.

Methods: Thirty-one patients aged 6 to 12 years newly diagnosed with BECTS were recruited. A psychometric assessment was performed before and during the follow-up of OXC monotherapy with Cognitive Computerized Task Battery, Depression Self-Rating Scale for children, Screen for Child Anxiety Related Emotional Disorders, and Quality of Life in Epilepsy-31 (QOLIE-31). The results of the assessments were compared to explore the effect of OXC monotherapy in patients with BECTS.

Results: Thirty children with BECTS completed the study. Five of ten cognitive test scores improved after treatment via OXC monotherapy, including visual tracing ($F = 14.480$, $P < 0.001$), paired associated learning (language) ($F = 6.292$, $P < 0.001$), paired associated learning (number) ($F = 9.721$, $P < 0.05$), word semantic ($F = 6.003$, $P < 0.05$), and simple subtraction ($F = 6.229$, $P < 0.05$). Of the neuropsychology data concerning the quality of life, statistically significant improvements were observed in emotion ($F = 4.946$, $P < 0.05$), QOLIE-social ($F = 5.912$, $P < 0.05$), and QOLIE-total ($F = 14.161$, $P < 0.001$).

Conclusions: OXC is safe and does not impair neuropsychologic functions, with no obvious mood burden on children with BECTS. Most importantly, OXC has positive impacts on children's perception of quality of life, especially in terms of happiness and life satisfaction.

Keywords: Epilepsy; Cognition; Psychosocial difficulties; Cognitive function; Benign epilepsy with centro-temporal spikes

Introduction

Benign epilepsy with centrotemporal spikes (BECTS) is the most common type of childhood idiopathic focal epilepsy, with the typical age of onset between 6 and 10 years of age. BECTS is estimated to account for up to 16% of all childhood epilepsy cases.[1] Most patients with BECTS achieve remission of seizures before puberty, but some children require anti-epileptic drugs (AEDs) for control of frequent clinical seizures. Previous reports revealed that various AEDs, such as barbiturates, vigabatrin, topiramate, and levetiracetam can inhibit seizures in patients with BECTS. However, a series of studies have revealed that BECTS is also associated with pervasive cognitive deficits and behavior problems, such as language function, memory, executive function, attention, and psychosocial difficulties.[2-5] Previous studies also revealed that children with BECTS scored significantly lower in tests on academic performance compared with healthy controls. Most of these studies attributed the poor academic performances to impairments in cognition, including visual attention, executive function, and others.[6] Since the patients are in a crucial stage of developing social strategies and acquisition of new skills, it is a key aim to select AEDs that do not further impair cognitive and psychosocial function. Furthermore, more attention should be paid to the improvement of comprehensive quality of life instead of only controlling seizures.

Oxcarbazepine (OXC) is an AED that is a ketoanalogue of carbamazepine with a more favorable pharmacokinetic and tolerability profile.[7] In most previous studies, OXC oral suspension was only shown to be safe and effective in

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pediatric epilepsy for seizure control with little adverse effects,[7-9] No cognitive effects were observed in these studies. Tzitiridou and colleagues were the first to include a cognitive evaluation in a study on OXC in BECTS.[10] Unfortunately, no psychosocial problems were evaluated. In Eun's study, more attention was put on cognitive effects and psychosocial problems in the evaluation of OXC.[11] However, children with various kinds of partial seizures were included. Patients with BECTS, as an idiopathic focal seizure, show a distinct spectrum of cognitive and psychosocial problems as described above. The effect of OXC on cognitive and psychosocial profiles of children with BECTS could not be inferred from this study. In the present study, we focus on the effects of OXC monotherapy on cognition, mood disorder, and quality of life to achieve a comprehensive understanding of the potential of OXC monotherapy in BECTS.

Materials and Methods

Subjects and study design

Thirty-one children (15 males, 16 females; mean age, 9.7 years; standard deviation [SD], 2.1 years) were recruited with typical clinical and EEG features of BECTS according to the International League Against Epilepsy classification. All participants were enrolled from Neurology Department, Children Hospital of Capital Institute of Pediatrics. Children with BECTS were selected based on the following criteria: (1) being newly diagnosed BECTS with brief rolandic seizure or secondary generalized seizure, no other seizure type indication than atypical BECTS, no more than 50% discharge index during slow-wave sleep period; (2) two or more seizures during the past three months that were judged to require therapeutic intervention; (3) drug naive; and (4) brain magnetic resonance imaging examination revealed no lesion. The exclusion criteria were as follows: (1) any previous exposure to drugs; (2) diseases of other systems such as cardiac, gastrointestinal, endocrine, renal, hematologic, or oncologic disorders; (3) epileptic structural brain abnormality in magnetic resonance imaging or any other neurologic disease; and (4) inability to independently complete the tasks. The mean age of epilepsy at onset was 8 years (range, 6–12 years).

OXC was initially administered at a dosage of 5 to 10 mg/kg/day, which was further increased to 30 mg/kg/day according to a set plan that was given to the parents along with the first prescription.

Neuropsychologic assessment

Computerized test battery

The neuropsychologic assessment battery included ten cognitive tests, which are described in detail as follows. The tests within the battery assessed multiple cognitive abilities: processing speed, spatial skills, calculation, language ability, intelligence, visual attention, memory, and learning ability. All tests were programmed using web-based applications from the Online Experimental Psychological System.[12] For all but one test, responses were indicated by pressing one of two keys ("P" or "Q") on a standard computer keyboard. For visual tracing, responses were indicated by a mouse click. Participant responses were automatically recorded to an online server.

Choice reaction time

This task was adapted from a previously described task that was used to evaluate processing speed. For each trial, a white dot was presented to the right or left of a fixation cross on a black screen. The localization of the dot was within 15° of the visual angle of the cross. Participants pressed the Q or P key to indicate the localization of the white dot. The task consisted of 30 randomized trials with the duration of the inter-stimulus interval randomly varying between 1.5 and 3.0 s.

Raven's progressive matrices

A simplified version of the Raven's progressive matrices test was used to assess general intelligence.[13] For this task, participants were asked to identify the missing segment that would complete a figure's pattern. Two candidate answers were presented side-by-side beneath each problem and participants were instructed to press Q if the missing segment was on the left and P if it was on the right. The test was time-limited (3 min) and consisted of 80 trials.

Visual tracing

The visual-tracing task was adapted from Groffman visual-tracing test.[14] Several curved lines were interwoven with one another in a square, starting from the left side and ending on the right. Participants were asked to track a particular line from beginning to end using only their eyes (ie, the use of a finger or cursor was prohibited) and to mark the correct endpoint. The degree of difficulty (ie, the number of lines) increased from trial to trial. There were 12 pictures used in each of the three trials. This task was also time limited.

Number magnitude comparison

The number magnitude comparison task was adapted from a number-comparison test used in previous studies.[15] Eighty-four pairs of single-digit Arabic numbers of varying sizes were presented in random order. For each pair, participants were asked to indicate the number of larger numerical magnitude while ignoring differences in the physical size of the numbers. Participants pressed the Q key to choose the answer on the left and the P key to choose the answer on the right. The magnitudes of the numbers were congruent, incongruent, or neutral in physical size (eg, if the pair of numbers was 3 and 8, the 3 could be physically smaller, larger, or the same size as the 8). In pairs of differently sized numbers, the ratio of the physical size of the two numbers was 1:2. The number comparison test consisted of three sessions (28 trials per session) that were separated by two 30-s rest periods. This task evaluated numerical processing.

Mental rotation

The mental rotation task was adapted from the mental rotation task used by Vandenberg and Kuse.[16] For each

trial, a three-dimensional image was presented on the upper half of the screen whereas two more images were presented on the lower half of the screen. Participants were asked to choose the image from the bottom of the screen that matched the image at the top. The matching image could only be identified by using mental rotation, whereas the non-matching image was a rotated mirror image of the target. The rotation angles of the matching images ranged from 15° to 345° (interval, 15°). Participants pressed the Q key to choose the image on the left and the P key to choose the image on the right. The mental-rotation test consisted of 180 trials. This test was time-limited (3 min) and evaluated spatial perception.

Simple subtraction

Ninety-two simple mathematical subtraction problems were presented. The minuends were 18 or smaller and the differences were single-digit numbers. Two candidate answers were presented below each problem. Participants were asked to press the Q key to choose the answer on the left and the P key to choose the answer on the right. For this task, each incorrect answer was within the range of the correct answer plus or minus 3 (ie, ±1, ±2, or ±3). This task was time-limited (2 min) and was used to evaluate mathematical ability.

Word semantics

A similar task was used in a previous study.[17,18] Materials in the task were adapted from textbooks used in primary schools from first to ninth grade. In each trial, a sentence missing one word was presented in the middle of the computer screen. Participants were asked to complete the sentence by selecting one of two candidate words presented below the sentence by pressing the Q key or the P key. The stimulus remained on the screen until participants responded. This task evaluated language ability.

Paired associative learning (language and number)

The paired associative learning task required the pairing of two items, with the first as the stimulus and the second as the response. Previous studies have shown that paired associative learning is related to memory and learning abilities.[19,20]

We formed pairs using two-character nouns and Arabic numbers, such as (tian# kong → season) and 9#3 → 2 8 (nine# three → two eight). Participants were first asked to try and memorize 15 word pairs and 15 number pairs. Each pair was presented for 10 s in the middle of the screen during the learning stage. During the test stage, participants were asked to indicate by a key press whether pairs were the ones that they had seen in the learning stage. Each trial lasted 3 s. The learning and test stages were repeated after the first series and the percentage of correct answers in the second test was analyzed. This task evaluated memory and learning abilities.

Quality of life survey for childhood epilepsy

Quality of Life in Epilepsy-31 (QOLIE-31) was used to assess the quality of life in epileptic children. The test was sub-divided into seven domains, including self-worrier for seizures, social function, emotional status, cognition, energy/vitality, health perceptions, and general life satisfaction.[21] The overall quality-of-life scoring scale was calculated from the 31 items, with higher scores representing better quality of life.

QOLIE-31 was revised with several items for the purpose of practical use in Chinese children, with high reliability and validity results.[22]

Depression and anxiety scale

Depression self-rating scale for children and the Screen for child anxiety-related emotional disorders were chosen for the evaluation of the anxiety and depression state.

Depression self-rating scale for children was developed by Birleson[23] with good reliability and validity. Screen for child anxiety-related emotional disorders was introduced by Birmaher *et al*[24] with good retest reliability and discriminative validity. With the Chinese versions of both assessments, high reliability, and validity were also achieved in Chinese clinical practical use.[25]

Procedure

All participants were tested with the computerized test battery before and after 346 ± 226 days of OXC monotherapy as described below. OXC was adjusted for each individual based on clinical requirements. Written informed consent was obtained from parents of all subjects before admission to the study.

All participants were tested with the computerized test battery before the beginning of OXC monotherapy as baseline data and were re-evaluated after the therapy. The battery of tests was administered to patients in two 45-min sessions in an examination room. Test procedures were presented on a computer screen and instructions were given orally. For each test, the participants received instructions first. This was followed by a practice session. The practice session for each task consisted of either four or six trials, which were similar to those used in the formal test. The computer provided the child with feedback on the screen after each practice trial. The feedback for correct responses was "Correct! Can you go faster?" The feedback for incorrect responses was "It is wrong. Try again." Children could ask the examiners any question that they had during the practice session. After the children finished the practice session and had no more questions, they could press any key to begin the formal test. The tests were administered in the same order for all participants. Each participant was monitored by one examiner who was familiar with the standardized testing procedures. Depression and anxiety scales and quality of life in epilepsy scales were also completed before and after OXC treatment.

Statistical analysis

For all tests except the choice reaction time test, the corrected scores were calculated by subtracting the number of incorrect responses from the number of correct

Table 1: The mean scores in depression and anxiety tests for children with BECTS before and after OXC treatment ($n = 31$).

Tasks	Pre-treatment	Post-treatment	*F*	*P* value	*F* after correction	*P* value
Depression	11.19 (3.69)	10.45 (3.91)	0.382	0.541	1.014	0.322
Anxiety	19.74 (10.17)	18.84 (9.15)	0.740	0.397	0.033	0.856

Data are expressed as mean (standard deviation). The *F* values represent the ANOVA between pre-treatment and post-treatment. The *F* after correction represents the ANOVA between pre-treatment and post-treatment with time interval as a covariant. BECTS: Benign epilepsy with centrotemporal spikes; OXC: Oxcarbazepine; ANOVA: Analysis of variance.

Table 2: The mean test scores before and after OXC treatment for children with BECTS ($n = 31$).

Tasks	Pre-treatment	Post-treatment	*F*	*P* value	*F* after correction	*P* value
Choice reaction time	568.65 (157.32)	538.10 (141.48)	1.607	0.22	0.374	0.546
Number magnitude comparison	48.58 (32.54)	58.97 (29.62)	2.244	0.15	1.350	0.255
Mental rotation	9.84 (8.90)	13.29 (10.00)	4.217	0.05	2.876	0.101
Paired associative learning (language)	11.19 (3.69)	10.45 (3.91)	6.292*	<0.001	0.289	0.595
Paired associative learning (number)	15.87 (9.05)	21.44 (3.17)	9.721†	0.01	0.846	0.600
Word semantics	14.77 (9.97)	18.74 (10.33)	6.003†	0.02	1.063	0.311
Simple subtraction	29.00 (12.39)	33.29 (9.50)	6.229†	0.02	0.079	0.780
Number serial completion	5.58 (5.86)	7.34 (6.15)	1.292	0.27	1.829	0.187
Raven's progressive matrices	12.87 (8.61)	13.16 (11.27)	0.018	0.90	0.149	0.702
Visual tracing	7.00 (6.42)	11.16 (5.83)	14.480*	<0.001	0.846	0.365

Data are expressed as mean (standard deviation). The *F* values represent the ANOVA between pre-treatment and post-treatment. The *F* after correction represented the ANOVA between pre-treatment and post-treatment with time interval as a covariant. * $P < 0.001$. † $P < 0.05$. BECTS: Benign epilepsy with centrotemporal spikes; OXC: Oxcarbazepine; ANOVA: Analysis of variance.

responses to control for the effect of guessing. For the choice reaction time test, each participant's median reaction time was calculated. Analysis of variance was conducted to test differences between pre-treatment neuropsychologic performances and post-treatment performances. The time interval was used as a covariant to eliminate the impact of time intervals. In all analyses, results were judged as being statistically significant if the *P* value was smaller than 0.05. Statistical analyses were performed using SPSS 21.0 (IBM, Armonk, NY, USA).

Results

Cognition

Mean scores and standard deviations (SDs) for all cognitive tasks scores before and after treatment of OXC are summarized in Table 1. Statistically significant improvements after treatment were observed in visual tracing ($P < 0.001$), paired associated learning (language) ($P < 0.001$), paired associated learning (number) ($P < 0.05$), word semantic ($P < 0.05$), and simple subtraction ($P < 0.05$). With time interval as a covariant, no deterioration in the neuropsychology test scores (*F* after correction) was observed after the OXC monotherapy [Table 2].

Depression and anxiety

Neuropsychologic scores concerning depression and anxiety revealed no significant differences between before and after OXC treatment [Table 1].

Quality of life

Mean (SD) and *t* test of scores in quality of life in epilepsy scale for children with BECTS before and after treatment are tested. Significant improvements were demonstrated in QOLIE-OQL, QOLIE-emotion, and QOLIE-total (mean value: 58.61 ± 7.32 *vs.* 54.00 ± 9.21, $F = 5.355$, $P = 0.03$; mean value: 54.16 ± 7.05 *vs.* 50.06 ± 6.06, $F = 6.323$, $P = 0.02$; mean value: 59.45 ± 34.07 *vs.* 56.84 ± 4.84, $F = 8.519$, $P = 0.01$) [Figure 1]. With time interval as a covariant, significant improvements were found in QOLIE-emotion, QOLIE-social (mean value: 54.16 ± 7.05 *vs.* 50.06 ± 6.06, $F = 4.946$, $P = 0.03$; mean value: 59.00 ± 3.32 *vs.* 57.35 ± 4.35, $F = 5.912$, $P = 0.02$). Marked improvements were revealed with QOLIE-total (mean value: 59.45 ± 34.07 *vs.* 56.84 ± 4.84, $F = 14.161$, $P < 0.001$). No obvious detrimental effects were found in QOLIE-SW, QOLIE-OQL, QOLIE-energy, QOLIE-cognition, and QOLIE-medicine (mean value: 56.77 ± 8.313 *vs.* 52.97 ± 8.10, $F = 2.666$, $P = 0.11$; mean value: 58.61 ± 7.32 *vs.* 54.00 ± 9.21, $F = 4.061$, $P = 0.05$; mean value: 48.16 ± 5.88 *vs.* 50.48 ± 7.97, $F = 1.986$, $P = 0.17$; mean value: 58.38 ± 5.22 *vs.* 56.71 ± 5.42, $F = 0.672$, $P = 0.42$; mean value: 60.48 ± 5.78 *vs.* 60.32 ± 5.14, $F = 0.576$, $P = 0.45$).

Discussion

We compared the distinctive cognitive test scores before and after OXC treatment. Different levels of progress were observed among these children, especially with respect to visual tracing, paired associative learning, and mental rotation. These cognitive tests require comprehensive cogni-

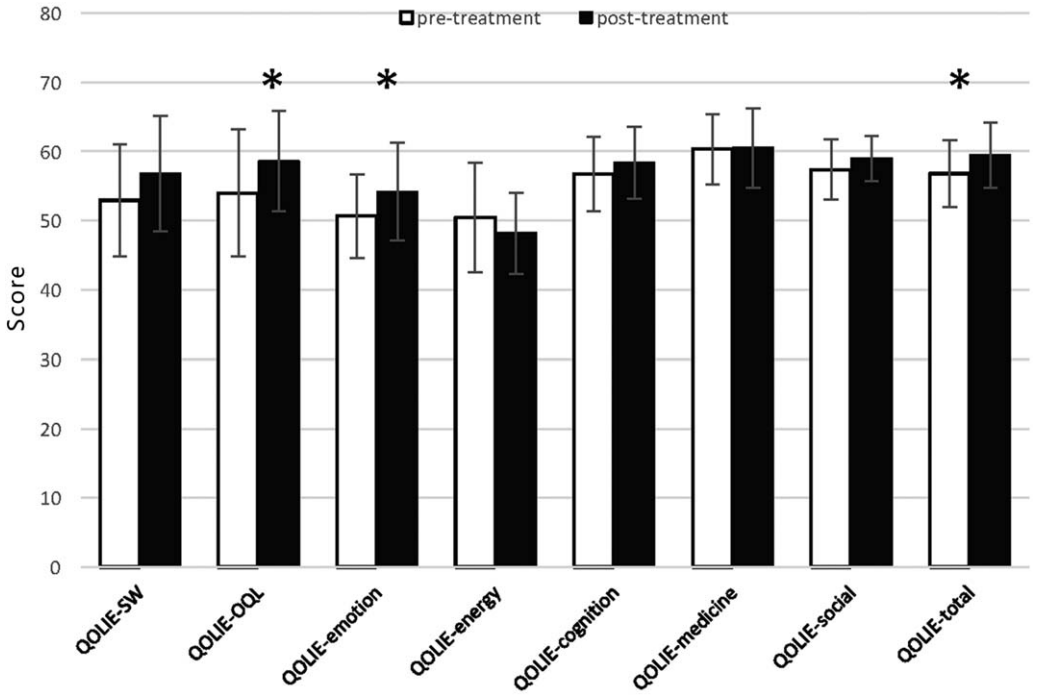

Figure 1: Comparison of mean (standard deviations) and *t* test scores in Quality of Life in Epilepsy scale for children with BECTS before and after treatment. Significant improvements were demonstrated in QOLIE-OQL, QOLIE-emotion, and QOLIE-total. $^{*}P < 0.05$. BECTS: Benign epilepsy with centrotemporal spikes; QOLIE: Quality of Life in Epilepsy.

tive abilities such as visual function, executive function, and attention. Previous studies revealed that OXC improves the performance in cognitive function both within healthy adult volunteers and epilepsy patients.[26] In our study, controlling for the time-interval effect, no detrimental effects were observed in these childhood patients with BECTS.

In a previous study with the same computerized test battery, cognitive deficits revealing in children with BECTS include spatial ability, calculation, and execution function.[22] In the current study, we found no further impairments in these cognitive functions by OXC treatment. In contrast, we observed even a mild improvement in simple subtraction, indicating moderate protective effects of OXC on cognitive functions.

In our study, no significant differences were observed in both depression and anxiety scores before and after OXC treatment. No obvious mood burden was observed in children with BECTS during the long treatment process. According to previous studies, many AEDs show associations with the occurrence of depressive symptoms, such as barbiturates, vigabatrin, and topiramate.[27] Although levetiracetam, the first choice of treatment in various types of childhood epilepsy, was shown to have little side effects, it still increases the risk of depression.[28] For children with BECTS who are still developing and studying, being in a good mood without symptoms of depression is beneficial for their development. Furthermore, for those children already trapped in depression or have the tendency for depression, OXC was, therefore, recommended to avoid depression and anxiety for better life quality.

Cognitive and behavioral issues may be the most frequent and intrusive manifestation of epilepsy.[29] BECTS is an age-dependent epilepsy syndrome, which has the tendency of remission of seizures and rolandic discharges after puberty. In addition to controlling the seizures, the optimal treatment strategies for patients of BECTS should emphasize the reduction of side effect on cognition and neuropsychology.

Quality of life has been defined by the World Health Organization as a reference to a person's wellbeing and the individual's perception of their position in life.[30] In our research, scores of quality of life were also improved after OXC treatment, which includes the QOLIE-emotion. Some studies revealed that OXC has potentially mood-stabilizing benefits.[31] Another study showed the efficacy and safety of OXC as adjunctive therapy in 18 patients with bipolar disorder who had not responded satisfactorily to lithium. In three responders to OXC as adjunctive therapy, mood stabilization was maintained for at least four consecutive months.[26] The present results suggest that some patients may benefit from OXC as a mood stabilizer. As children with BECTS are in a state establishing self-esteem and acquiring vast amounts of knowledge, mood stabilization is important for their life.

In addition to QOL-emotion, we also observed significant improvements in QOL-total. Due to the complex nature of epilepsy and its usually chronic course, various factors can have large effects on a person's perception of quality of life, happiness, and life satisfaction. In our QOL, we evaluated seven aspects, for example, cognition, medicine, energy, and emotion. In addition to emotion, our data also revealed a mild enhancement for social and QOL after OXC treatment of OXC, indicating that OXC treatment may improve the quality of life overall and not only for emotion.

Our data reveal that OXC is safe and protective for neuropsychologic functions, with no obvious mood burden on children with BECTS. Most importantly, OXC has a positive impact on patients' perception of quality of life, especially regarding happiness and life satisfaction.

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Conflicts of interest

None.

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