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Effects of levetiracetam as an add-on therapy on cognitive function and quality of life in patients with refractory partial seizures

Bo Zhou [a,b,1], Qin Zhang [a,1], Linyu Tian [a], Jun Xiao [b], Hermann Stefan [c], Dong Zhou [a,*]

[a] Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, People's Republic of China
[b] Department of Neurology, People's Hospital of Sichuan Province, Chengdu, Sichuan 610072, People's Republic of China
[c] Department of Neurology, Epilepsy Center Erlangen, University of Erlangen-Nuremberg, Nuremberg, Germany

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Abstract

This study comprised two phases and evaluated the effects of levetiracetam (LEV), as an add-on treatment, on cognitive function and quality of life (QOL) in patients with refractory partial seizures. The short-term phase employed a randomized, double-blind, placebo-controlled design including an 8-week baseline period, 4-week titration interval, and 12-week period at the maximum LEV dose (1500 mg twice daily). The long-term phase was an open-label study in which the maximum LEV dose was administered for another 24 weeks. Neuropsychological tests and the 31-item Quality of Life in Epilepsy (QOLIE-31) inventory were administered at baseline, at the end of the short-term phase, and at the end of the long-term phase. Twenty-four eligible patients entered into the final phase. After short-term LEV treatment, performance time on the Wisconsin Card Sorting Test (WCST) and Delayed Logic Memory significantly improved for the patient group, but not the control group. Subscale scores on the QOLIE-31, including scores on Cognitive Functioning and Social Function, also improved only for the LEV group. At the end of the long-term phase, these improvements were maintained, and both groups performed better in more areas, as measured by the Trail Making Test, WCST, and Delayed Visual Memory in the neuropsychological battery and the QOLIE-31 subscales Overall QOL and Health Status. Thus, as an adjunctive therapy, LEV did not negatively affect and, in a way, improved cognitive function and QOL in patients with medically refractory partial seizures. Some of these improvements may be maintained during long-term treatment.

Keywords: Levetiracetam; Partial seizures; Cognitive function; Quality of life

1. Introduction

Levetiracetam (LEV), a novel broad-spectrum antiepileptic drug (AED), has been used as an add-on therapy in focal seizures with or without generalization [1,2]. It has been reported that LEV has a favorable pharmacokinetic profile and a low incidence of side effects or interactions with other AEDs [3]. Although assessment of health-related quality of life (HRQOL) has become routine during the development of new AEDs and cognitive effects constitute one of the considerations in the choice of AEDs, to date, only a few articles describing researches on the effects of LEV on cognitive function [4,5] and quality of life (QOL) [6–9] have been published. Moreover, the results obtained from studies on the impact of LEV on cognition were based on a single-blind or open-label trial, which has its own limitations. To get clearer and more reliable answers, double-blind or placebo-controlled trials are further needed [4,5].

In the present study, our goal was to assess the short-term (randomized, double-blind, placebo-controlled study for 12 weeks) and long-term (open-label study of LEV for another 24 weeks) effects of LEV, as an adjunctive treatment, on cognitive function and QOL in patients with refractory partial seizures. We tried to combine the results of objective neuropsychological tests with self-perceived

* Corresponding author. Fax: +86 28 8542 2549.
E-mail address: zhoudong66@yahoo.de (D. Zhou).
[1] The two authors contributed equally to this article.

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HRQOL to get a better understanding of the efficacy of LEV.

2. Methods

2.1. Subjects and methods

Outpatients with epilepsy from the Epilepsy Clinic of the Department of Neurology, West China Hospital, between 1 July 2004 and 31 May 2005, were screened. Enrollment, regardless of gender, was limited to adult patients (aged 16–70 years) whose partial-onset seizures (simple or complex partial with or without secondary generation, according to the International League Against Epilepsy (ILAE) classification) were poorly controlled by at least one first-line AED at the time of the study. Poor control was defined as having a minimum of eight seizures during the 8-week baseline period with a minimum of two seizures during each 4-week period [6–8]. Participants were not seriously intellectually disabled (IQ $\geqslant$ 80), and could read and comprehend the questions. Patients with progressive neurological disorders, severe internal organ diseases, pregnancy, alcohol addiction, or drug abuse were excluded.

The study period consisted of two phases. In the first phase, which comprised an 8-week baseline period, a 4-week interval of titration of LEV/placebo (500 mg twice daily in the first two weeks, 1000 mg twice daily in the third and fourth weeks), and a 12-week period at the maximum LEV/placebo dose (1500 mg twice daily), all patients were randomized into the LEV or placebo group by use of a random number table. Each eligible participant received an exclusive random number consecutively on entry into the study, and received treatment on the basis of this random number. In the second phase, all enrolled patients received the maximum LEV dose (1500 mg twice daily) for another 24 weeks. Other AEDs were kept at a stable dose throughout the study (Fig. 1).

The study was conducted according to Good Clinical Practice guidelines, the amended Declaration of Helsinki, and China clinical trial regulations, and was approved by the local ethics committee. Written informed consent from each patient was obtained before enrollment in the study. All study medications (LEV and placebo) used in the trial were supplied and packaged by UCB Pharma.

Electroencephalography (EEG) was performed at the eighth week of the baseline phase (i.e., Week 8) and at the end of the first phase (i.e., Week 24). The mean number of partial seizures per week was recorded as seizure frequency. As for differences between seizure frequency during the 12 weeks on medication (Weeks 13–24) and baseline (Weeks 1–8) seizure frequency, 100% reduction was considered as seizure-free, $\geqslant$75% reduction as notably improved, 50–75% reduction as effective, and <50% as ineffective.

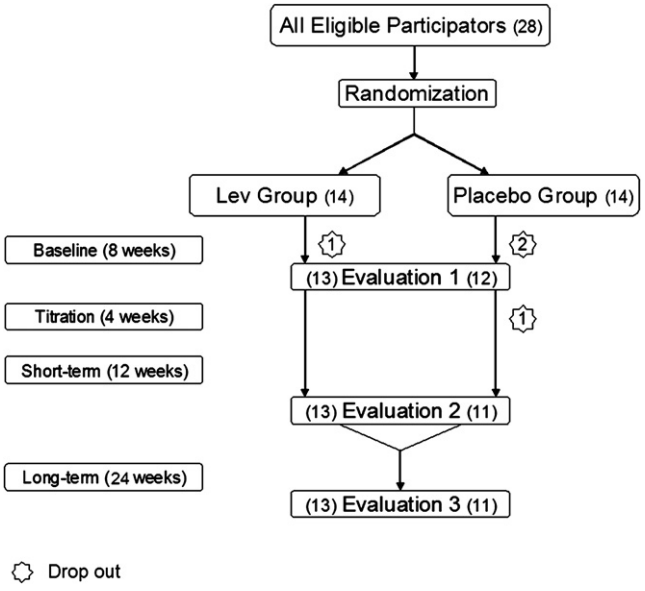

Fig. 1. Outline of the trial.

Cognitive function was assessed through a neuropsychological battery of tests (see below) and HRQOL was evaluated with the 31-item Quality of Life in Epilepsy (QOLIE-31) inventory at the baseline phase (i.e., Week 8), the end of the short-term phase (i.e., Week 24), and the end of the long-term phase (i.e., Week 48). The English-language QOLIE-31 was translated into the Chinese version according to international principles (series of forward and backward translations followed by reconcilable discussion) [10,11].

The neuropsychological battery consisted of nine representative tests chosen from the Chinese version of the Wechsler Adult Intelligence Scale—Revised (WAIS-RC) and some other tests commonly used to assess important cognitive functions [11]. Verbal Fluency is used to evaluate language fluency, as well as frontal dysfunction. The Trail Making Test (including Parts A and B) is primarily a test of motor speed and visual attention. The Wisconsin Card Sorting Test (WCST), a test of "set shifting," assesses the ability to display flexibility in the face of changing schedules of reinforcement; its completion relies on intact cognitive function including attention, working memory, and visual processing. Digit Symbol evaluates visual–motor coordination and motor and mental speed, whereas Digit Span measures working memory and attention. The Stroop Color–Word Interference Task is a test of vitality and flexibility of attention, and focuses on executive function mediated by the frontal lobe. Logic Memory, Visual Memory, and Calculation assess the capabilities as their names indicate. The higher the scores on these tests, the better is the neuropsychological performance, with the exceptions of the Trail Making Test, performance time on the WCST, and reaction time on the Stroop Color–Word Inference Task, for which lower scores indicate better results. Although the battery was applied three times during the study, its test and retest intervals were at least 16 weeks, and some considered this long enough to avoid practice effects, especially for the WCST [12].

QOLIE-31 [13], a self-administered questionnaire, was completed by patients. It includes seven subscales (Seizure Worry, Overall QOL, Emotional Well-Being, Energy–Fatigue, Cognitive Functioning, Medication Effects, and Social Function) and the Health Status item. Response can be scored to provide subscale scores and a total score, with a higher score representing better function. The Chinese version has been reported as having good validity and reliability [10,14].

2.2. Statistical analysis

Statistical comparison was performed with SPSS for Windows 11.0. Continuous variables with a normal distribution were analyzed by using paired t tests to investigate differences between baseline and posttreatment, or by using group t tests for independent samples to investigate the differences between two groups. When continuous variables showed an asymmetric distribution, the Wilcoxon rank sum test was performed. Categorical variables were analyzed using the χ^2 test. The significance level was set at $P < 0.05$.

3. Results

3.1. Patient demographics

Twenty-eight eligible patients were randomized into the LEV ($n = 14$) or placebo ($n = 14$) group. Four patients (one from the LEV group and three from the placebo group) withdrew from the trial due to noncompliance. Twenty-four patients completed the whole study. The demographics of patients are summarized in Table 1. The groups did not differ statistically significantly with respect to gender, age, education, seizure frequency, and number of concomitant drugs ($P > 0.05$). Although the placebo group had a mean duration