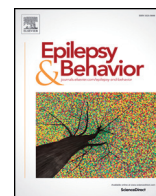




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Cannabidiol for treatment of refractory childhood epilepsies: Experience from a single tertiary epilepsy center in Slovenia

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ABSTRACT

Purpose: Refractory epilepsies in children present a major burden for patients and their families. Cannabidiol (CBD) has been suggested as a potential treatment for refractory epilepsies. The aim of this study was to evaluate the effectiveness of add-on therapy with CBD for the treatment of refractory childhood epilepsies.

Method: Patients with childhood-onset refractory epilepsy, treated at the tertiary epilepsy center of the University Children's Hospital Ljubljana, Slovenia, were included in the study. Add-on therapy with CBD was initiated once the child's epilepsy was categorized as pharmacoresistant to other antiepileptic drugs/therapies. The dosage of CBD was gradually increased to at least 8 mg/kg/day. The effect of CBD treatment was evaluated by the reduction in seizure burden and presence of side effects (positive and negative). Serial electroencephalography was performed in some children.

Results: Sixty-six patients were included in the analysis. Thirty-two (48.5%) patients had a more than 50% improvement regarding seizure burden, 14 of whom (21.2%) became seizure-free. None of the patients reported worsening of seizure frequency, but CBD had no effect in 15 (22.7%) patients. Some patients reported less vigorous seizures, shorter duration of seizures, shorter time to recovery, and other positive side effects of CBD treatment. Adverse effects were reported in 5/66 children.

Conclusions: In our cohort of patients, CBD was found to have potential benefits as add-on therapy for refractory childhood epilepsies, mainly by reducing seizure burden.

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1. Introduction

There is no simple and uniform definition of refractory (pharmacoresistant, intractable) epilepsy. In very broad and general terms, pharmacoresistance is the failure of seizures to come under complete control or acceptable control in response to antiepileptic drug (AED) therapy [1,2]. When AEDs fail, other treatment possibilities are available, such as ketogenic diet (KD), epilepsy surgery, vagal nerve stimulation, and, recently, treatment with extracts of cannabis containing cannabinoids [3–5].

The cannabis plant contains more than 100 cannabinoids that can have an effect on the human body through various mechanisms [6]. Cannabinoids that are derived from the plant are termed phytocannabinoids, and a wide range of synthetic cannabinoids has already been produced. The biological effects attributed to cannabis have mainly been linked to the phytocannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), both of which are present in cannabis in very high concentrations. However, other

cannabinoids are also present in cannabis in smaller amounts and are thought to be involved in the subtle modulation of medicinal effects (sometimes referred to as the entourage effect or synergy). This effect may be the result of their independent biological activity or through synergy with THC and CBD [7].

Compared with THC, CBD is frequently characterized as a nonpsychoactive or nonpsychotropic substance; however, these terms are inaccurate because CBD has prominent beneficial pharmacological effects on anxiety, schizophrenia, addiction, and possibly even depression [8]. A more accurate designation would be “nonintoxicating” substance as CBD is lacking the associated reinforcement, craving, compulsive use, and similar effects that are well-known for THC and that indicate drug abuse liability [8,9]. Until now, it has not been proven that CBD can be converted into THC in the human body, although under certain (extremely acid) conditions, this has been confirmed in “in vitro” studies [8]. In contrast to other newly developed AEDs, CBD remains an intriguing agent of unparalleled diversity of pharmacological effects without severe side effects [8]. Furthermore, there is a long list of new AEDs which have not improved the outcome of refractory epilepsies and show several side effects that influence the quality of life (QoL) of patients with epilepsies (as well as their families) nearly as much as the seizures themselves [10].

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At present, some clinical evidence exists that CBD can ameliorate epilepsy in both adults and children who are affected by refractory epilepsies, epilepsy syndromes, or epileptic encephalopathies and has a favorable side effect profile [10–12]. The only two randomized control trials published to date in peer-reviewed journals are trials on the efficacy of CBD for Dravet syndrome and Lennox–Gastaut syndrome [13, 14]. In the first study, 120 young adults with drug-resistant convulsive seizures due to Dravet syndrome were included. The median decrease in seizures in the treatment group was 38.9% versus 13.3% in the placebo group. In the second study (171 patients, aged 2–55 years), add-on CBD was found to be efficacious for the treatment of patients with drop seizures associated with Lennox–Gastaut syndrome and was generally well tolerated. For other indications such as tuberous sclerosis, phase 3 trials have also been completed, which suggests that CBD may also benefit patients with these syndromes [15]. Some anecdotal case reports describe dramatic improvement of seizure control [16,17]. It has also been shown recently that CBD may have a beneficial effect on a child's QoL, an effect which is independent of the seizure-reducing effect [18].

The main aim of this paper was to present our experience with a synthetic CBD preparation for treatment of the most severe cases of refractory childhood epilepsies in a single, third-level epilepsy center in Slovenia. We also describe particular cases where such treatment provided a significant improvement not only in the frequency and severity of the seizures but also in other aspects of the patient's wellbeing.

2. Materials and methods

In this retrospective study, electronic patient records of children, adolescents, and young adults who were given CBD preparation for treatment of refractory epilepsy in the period between February 1st, 2015 and July 31st, 2017 were reviewed. Patients were treated and followed up at the Department of Child, Adolescent and Developmental Neurology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia. The only Slovenian tertiary level epilepsy unit is a part of our department.

The CBD preparation we have used consisted of crystalline cannabidiol powder (>98% pure) produced by Bionorica®. This powder was mixed by our hospital pharmacy into an oily solution containing 100 mg of CBD per 1 ml. Cannabidiol was used exclusively as an add-on therapy. The request for CBD treatment was always raised by the child's parents who learned about this possibility from other parents or the media. Before the initiation of CBD treatment, basic blood tests were performed (full blood count, electrolytes, liver enzymes, ammonia). After the introduction of the CBD preparation into the treatment, all of the patients continued to receive their previous AEDs for at least 6 months before potential further modifications of treatment or discontinuation of CBD.

The starting dosage of CBD was 1–3 mg/kg/day, raising gradually each week up to a dosage that controlled the seizures or to a maximum of 16 mg/kg/day. Patients were clinically followed up regularly, at least 2 times during the initial 6 months of treatment. Once the CBD treatment has reached the therapeutic dosage, we repeated blood investigations and a follow-up electroencephalogram (EEG), and if clinically relevant, we repeated this at further follow-ups.

Seizure control was categorized as follows: no seizures, >90% improvement, 75%–90% improvement, 50%–75% improvement, 25%–50% improvement, <25% improvement, no improvement, and worsening of seizures, as reported by parents. The number of seizures per period of time was translated into categories of percentage of improvement. Parents were asked to report any possible side effects and any other (beneficial) effects.

Statistical analyses were performed using GraphPad Prism version 7 (GraphPad Software Inc., La Jolla, CA, USA) and SPSS software version 24 (SPSS Inc., Chicago, IL, USA). To assess the relationship between a particular AED and an outcome, Pearson's chi-square test was used. As data

were not normally distributed, the Mann–Whitney *U* test was used for 2-group comparisons to get exact 2-tailed *p* values. Graphical data are presented as median with 95% confidence intervals (CI). A *p* value of <0.05 was considered as statistically significant.

All parents signed informed consent at the start of the treatment with CBD. The study was approved by Slovenian National Ethics Board No. 103/10/13.

3. Results

We have identified 70 patients who met the study inclusion criteria. Of these, 39 were boys (57%) and 31 were girls (43%); M/F ratio was 1.3:1. The median age of inclusion was 8.0 years, ranging from 0.5 year to 23.0 years. During the study period, 2 patients died: one had multiple cavernomas and died suddenly during sleep while the other had a confirmed genetic epileptic encephalopathy (SPTAN1 mutation) and died because of bronchopneumonia. Two patients were lost to follow-up. The final number of patients included in the analysis was 66.

The etiologies of epilepsies were as follows: a known chromosomal/genetic abnormality in 14 patients, morphological brain abnormality in 10 patients, hypoxic–ischemic brain injury in 6 patients, metabolic/mitochondrial disorder in 5 patients, known epileptic syndrome in 4 patients, postinfectious brain injury in 2 patients, and an undefined etiology for a refractory epilepsy in 25 patients. Of the patients with a known epileptic syndrome, 2 patients had Lennox–Gastaut syndrome, one had Landau–Kleffner syndrome, and one had Ohtahara syndrome. None of the patients in our cohort had Dravet syndrome, for which CBD therapy has been previously shown to be beneficial [19]. Patients were followed up for a median of 14.0 months, ranging from 6.0 to 29.3 months.

Patients were treated with 1–14 (median: 3) AEDs and/or a vagus nerve stimulator (VNS) prior to start of CBD treatment. Cannabidiol was added to 1–4 (median: 2) AEDs and/or VNS at the start of CBD treatment. Fig. 1 represents antiepileptic therapy used at the start of CBD treatment. Out of all patients included in the study, VNS was implanted in 4. The parameters of the VNS were not changed 6 months prior to or after the initiation of CBD treatment. None of the patients were on KD at the onset of CBD treatment although several have been on KD before the introduction of add-on CBD treatment.

The median starting dosage of CBD was 2.5 mg/kg/day (range: 0.5–5.0 mg/kg/day), divided into two daily dosages. In infants below 2 years of age, the daily dosage was divided into three dosages. The median therapeutic dosage was 8.3 mg/kg/day (range: 3.0–22.0

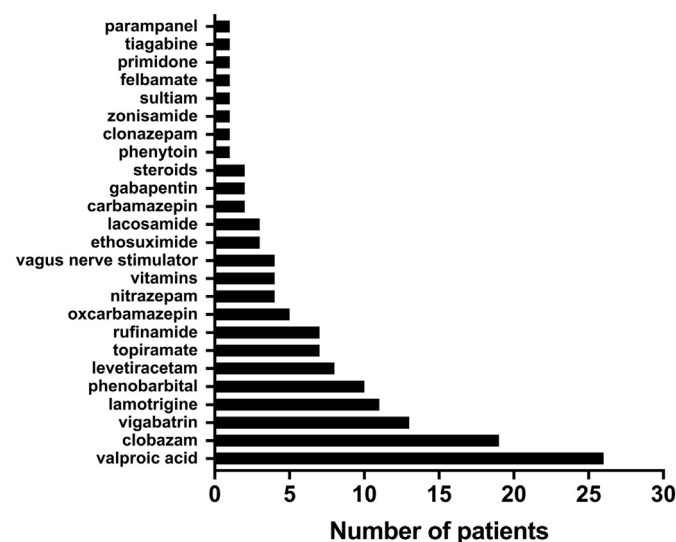


Fig. 1. Number of patients treated with a particular AED or VNS at the onset of CBD treatment.

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