ARTISANAL CANNABIDIOL AS ADJUNCT TREATMENT FOR REFRACTORY EPILEPSY: A BRAZILIAN EXPERIENCE / CANABIDIOL ARTESANAL COMO TRATAMENTO ADICIONAL PARA EPILEPSIA REFRATÁRIA: EXPERIÊNCIA BRASILEIRA

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ABSTRACT Introduction: The treatment of refractory epilepsy in childhood is a challenge in medical practice. The authors describe the experience with cannabidiol (CBD) use in patients with refractory epilepsy. Objectives: To evaluate the response to CBD treatment in the control of epileptic seizures, as well as their tolerability and side effects. Methods: A retrospective descriptive, series of cases study was performed, with data collected from 24 patients aged 1 to 45 years, diagnosed with refractory epilepsy, and who used CBD as adjunctive therapy. The CBD dose used ranged from 2.5mg/kg/day to 14mg/kg/day, with an average of 6.3mg/kg/day. Results: Of the twenty-four patients analyzed, there was a reduction in seizure frequency in 19 patients (79.%), and of these, five patients (20.8%) presented seizure reduction between 50-79% (moderate response), ten patients (41.6%) presented seizure reduction between 80-99% (marked response) and four patients (16.6%) presented complete seizure resolution. On the other hand, five patients (20.8%) did not respond to CBD treatment. Of these, one patient had no change in seizure pattern, and four patients (16.6%) had increased seizure frequency. Among the positive aspects of the use of CBD was a reduction in the number of hospitalizations, reduction in polytherapy (70% of cases) and improvement in some cognitive and behavioral aspects. The adverse effects mentioned were considered mild. Conclusion: CBD represents a promising alternative in refractory patients to conventional anticonvulsants.

KEYWORDS Anticonvulsants, Cannabidiol, Cannabis sativa, Epilepsy, Pharmacological Treatment

Introduction

Drug-refractory epilepsy is defined as failure to control epileptic seizures by at least two anticonvulsant drugs, appropriate for the patient's type of epilepsy, used in monotherapy or in combination treatment, administered at well tolerated therapeutic doses.[1] Despite the various therapies available, including new antiepileptic drugs, neurosurgical procedures and ketogenic diet, the number of patients with refractory seizures to the treatment remains high, affecting approximately 30% of patients.[2] For this reason, there is a demand for the development of new anticonvulsant option that are effective and have safety profile, especially in the pediatric population. In this scenario, cannabinoid derivatives are a potential strategy, as they have a distinct action mechanism from conventional anticonvulsant drugs and appear to have side effects well tolerated.

Cannabis sativa has been applied for medicinal purposes for thousands of years.[3] Mechoulam and colleagues have isolated its main components and chemical structures, and were also pioneers in the first CBD trial with treatment for refrac-

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tory epilepsy.[4] Among cannabinoids, the most studied compound is cannabidiol (CBD), due to its anticonvulsant property, especially for the absence of psychoactive effects, and delta 9-tetrahydrocannabinol (THC), its main psychoactive compound.

The mechanism of action of CBD is complex and still poorly understood. Despite presenting low affinity to CB1 receptors, CBD acts in other ways: it facilitates endocannabinoid signalling and acts on multiple targets, such as blocking anandamide enzymatic hydrolysis, increases 5-HT1a receptor activity, alpha-3 and alpha-1 wisteria receptors, acts on type 1 vanilloid receptors and has anti-inflammatory and anti-oxidant effects. It is also able to influence neuronal excitability by modulating voltage-dependent calcium channels, reducing glutamate release, which explains its action in the control of epileptic seizures.[5]

However, THC acts as a partial agonist of cannabinoid receptors CB1 and CB2, and exerts proconvulsant or anticonvulsant effects, depending on the dose and the experimental model used [6,20]. CBD is metabolized by the liver through cytochrome P450 enzymes, excreted in faeces and, to a lesser extent, in urine.[6]

Over the last decades, CBD has become the target of several experimental studies, revealing a wide spectrum of pharmacological properties, ranging from analgesic and immunomodulador action, to treatment of epilepsy, schizophrenia, Parkinson's disease and Alzheimer's disease5,6. Given this scenario, this paper aims to present the authors' experience with the use of CBD in the treatment of patients with refractory epilepsy and their results.

Methods

A descriptive retrospective, series of cases study was conducted to determine the efficacy and tolerability of the use of CBD in patients with refractory epilepsy. The study was approved by the FHEMIG ethics committee.

The inclusion criteria was patients who presented refractory childhood-onset epilepsy, who were treated with CBD as adjunct therapy for seizures control, without modifying the other antiepileptic drugs in use in the three months prior to the beginning of CBD use, as well as in the period of maintenance of use.

Data collection was performed through review of medical records, medical consultations and quarterly clinical reassessment of all patients from March 2016 to May 2017. Patients were informed of their participation and inclusion in the study. A questionnaire was applied, according to type of seizure, epileptic syndrome and etiology of epilepsy (genetic or structural). Data were collected regarding the age of seizures onset, number of drugs used before starting CBD treatment, monthly number of seizures described in the medical records and also based on parents information at the time of medical evaluation, before and after the use of CBD, doses and formulations used, presence of side effects, clinical picture of the patient regarding acquisitions in neuropsychomotor development before and after the use of CBD and other positive aspects observed by family members in addition to seizure control.

The patients were between 1 and 45 years old: 22 children (1 to 19 years old) and 2 adults (29 and 45 years old). All patients used anticonvulsants in optimal doses before starting CBD as adjuvant. The age of onset of epileptic seizures ranged from 2 months to 6 years. The minimum dose of CBD used was 2.5 mg/kg /day, and the maximum was 14 mg/kg/day (average:6.3 mg/kg/day). The doses were divided into two shots, and were gradually titrated according to tolerance and seizure control. The duration ranged from 2 to 37 months, with an average of 19.4 months. Most patients were already using CBD at the beginning of the study data collection, for this reason the period of use differs from the period of data collection.

All compounds used by patients were industrialized and had purified CBD extracts with a maximum THC content of 0.3%. They had several different formulations and brands. Patients acquired CBD, through import from the USA, following the legal procedures required by the National Health Surveillance Agency (ANVISA).

To assess the effectiveness of CBD, the monthly average of epileptic seizures in the three months prior to the initiation was calculated, and compared with the average of seizures reported by parents in the last three months of CBD use at the time of his last routine outpatient medical evaluation. In patients who had used CBD for a shorter period (less than three months) or who were verified in their routine medical evaluation that the treatment was discontinued (due to lack of response or seizure worsening), the average frequency of seizures was calculated based on the period of CBD use and compared with the mean frequency of seizures that preceded its use in a similar time.

Anticonvulsant drugs were not modified during the evaluation period. Descriptive data from our series are summarized in Table 1. To discuss the results, a literature review was conducted with articles indexed in the English and Portuguese MEDLINE and LILACS database, published between 2007 and 2020 with the keywords "epilepsy", "treatment", and "cannabidiol".

Results

Of the 24 patients analyzed, 79.2% of our sample (19) showed good response to CBD with reduction in the monthly frequency of epileptic seizures. The percentage in seizures reduction according to type, epileptic syndrome, structural or genetic ethology are detailed in Tables 2 and 3. Among the cases with satisfactory response to CBD use, three patients made concomitant use of ketogenic diet. The adverse effects found are summary in Table 4.

Discussion

Devinsky´s et al.[7] conducted a prospective study using CBD in 214 patients with refractory epilepsy. The dosage used was 2-50mg/kg/da. Adverse effects were observed in 79%: drowsiness, diarrhea, appetite reduction, fatigue, seizures, increased appetite and status epilepticus. Regarding the analysis of CBD efficacy, 64% of their sample, 39% had a 50% reduction in seizure frequency, 21% had a 70% reduction, and 9% had a reduction above 90%. Most patients were using clobazam, so it is postulated that the interaction of CBD with this drug may have influenced the analysis of its efficacy.

Among the likely explanations for the interaction of CBD with clobazam is that it is metabolised by enzymes of the hepatic microsomal complex. CBD is known to be metabolised in the liver and has an inhibitory effect on these enzymes, and it is therefore assumed that elevation of a clobazam (desmethylclobazam) metabolite level may occur, which may potentiate the antiepileptic and sedative effects of this drug[8,20].

There may be interaction between valproate and CBD, enhancing the effects of valproate hepatotoxicity with transaminase elevation in patients who used this association. Studies evaluating CBD's drug interaction have also shown increased serum levels of topiramate, rufinamide, zonisamide and eslicarbazepine. However, except for desmethylclobazam, the levels

of the other drugs were still within acceptable therapeutic values[9]. However, when CBD is used with liver enzyme-inducing drugs such as carbamazepine and phenytoin, these drugs may reduce serum levels of CBD[10].

Tzadok et al (2016)[11] conducted a retrospective study that included 74 patients with refractory epilepsy. The dosage used was 1-20mg/kg/day. An improvement in seizure control was found in 89%, being 18% reported a reduction in seizure frequency of 75-100%, and 34% of patients had a reduction of 50-75%, 12% had a reduction by 25-50%, 26% of patients had a reduction of less than 25% and 7% had seizure frequency worsening.

Improvements in alertness, behavior, language, communication, motor control and sleep have also been reported. Adverse reactions observed were drowsiness, fatigue, gastrointestinal disorders and irritability, which led to withdrawal of CBD in 5 patients.

Devinsky et al. (2017) [12] conducted a double-blind randomized clinical trial among patients with Dravet's Syndrome (120). Of these, 108 completed the study using CBD (52) versus placebo (56). Staggered doses of CBD up to 20mg/kg/day. There was more than 50% reduction in seizure frequency in 43% of patients on CBD versus 27% in the placebo group. These findings were statistically significant in favor of CBD in seizure control compared to the placebo group.

Some adverse effects observed: drowsiness, diarrhea, appetite reduction, fatigue, vomiting, fever, respiratory tract infection, seizures and lethargy. This same author in 2018 [13] conducted a double-blind clinical trial involving patients with Lennox Gastaut Syndrome (225), randomized into groups using doses of CBD up to 10 mg/kg day (73), 20 mg/kg/day (76) and placebo (76). The avarage percentage reduction in the number of atonic seizures relative to baseline in the 20mg/kg/day CBD dose group was 41.9%, while the 10mg/kg/day CBD dose group was 37.2% and in the placebo group was 17.2%. The same side effect profile was observed more frequent in the group using 20 mg/kg/day. 9% of patients using CBD had increased liver transaminase levels; this finding is more frequent in the group that used CBD doses of 20mg/kg/day and concomitant use of valproate.

In our sample, we obtained a satisfactory response with a reduction in seizure frequency in 19 (79%) of the 24 patients analyzed. We emphasize that of these, 4 (16.6%) had complete seizure resolution (Seizure free), 10 (41.6%) had marked reduction (80 to 99%) in seizure frequency, and 5 (20.8%) had moderate reduction (50 to 79%).

Four children with West syndrome had a satisfactory response to CBD use: 2 had complete seizure control and 2 had a marked reduction in seizure frequency (80-99%). Studies with the use of CBD for the treatment of West Syndrome are still scarce in the literature14 and our study points to a potential role of CBD in the treatment of this epileptic syndrome. Well-controlled studies on the use of CBD in West Syndrome are needed, as this epilepsy especially affects children under two years of age and is an extremely devastating type of epilepsy for the child's neurological development, whose therapeutic arsenal is scarce, especially in patients who do not respond to vigabatrin and/or corticosteroid therapy.

Three patients with Lennox Gastaut Syndrome: 2 had a sharp reduction in seizure frequency (80-99%) and 1 had no response to CBD. This patient had congenital toxoplasmosis sequelae with severe brain structural injuries. In the other 2 cases analyzed, 1 patient had autism associated with chromosome 15 microdeletion and another had polymicrogyria. In these 2 patients, we found a moderate response to CBD especially in the control of atonic seizures, as described in the main clinical trials that evaluated the efficacy of CBD in this epileptic syndrome[13,14].

Of the 2 cases of Dravet's Syndrome (both SCN1A), one patient had a seizure frequency reduction between 80-99% (marked response) and the other between 50-79% (moderate response); never again had hospitalizations due to status epilepticus. In one patient, there was complete resolution of atypical absences and eyelid myoclonus that were daily and frequent before the introduction of CBD.

The case of Landau Kleffner Syndrome that had a reduction by 80-99% (marked response), improvements in regarding interaction and perception. The patient with Doose Syndrome had a worsening seizure pattern using CBD, and we opted to withdrawal it, so CBD was used for only two months.

We used low doses of CBD when compared with other studies in the literature[7,11,12,13,15,16] (average dose of 6.3 mg/kg/day and maximum dose of 14 mg/kg/day), we had a mild side effect profile, and CBD was well tolerated in most patients. Only three patients were taking clobazam concomitantly, so it was not possible to attribute the efficacy of CBD in combination with this drug as observed by other authors.

Among the 5 patients with no response to CBD (20.8%), 4 had epilepsy due to structural injury, one case with Lennox Gastaut and 3 with predominantly focal seizures. Although our sample was small, we observed that most patients with no response to CBD had severe structural lesions and refractory focal epilepsy, which could point to a lower efficacy of CBD in these cases.

A patient with a previous history of epilepticus status prior to the use of CBD had no response and presented a status epilepticus after six months of use. This patient has severe brain injury due to viral encephalitis sequelae, so the causal link between the use of CBD and the occurrence of epilepticus status could not be established.

The remaining patients also had their CBD removed due to lack of response or seizure worsening. However, one of the patients who presented worsening seizure frequency in the phase of CBD dose progression (7mg/kg/day) returned to the usual seizure frequency when the dose was halved. We observed significant patient improvement from the cognitive point of view and we decided not to discontinue the medication and to keep it in a lower dose, despite the failure to control the seizures. It was a child with focal seizures of secondary structural etiology to frontal polymicrogyria who had already undergone surgical treatment of epilepsy (lobectomy) without success in seizure control. The child presented autistic behavior with self-aggression and poor social interaction. The family members noticed an improvement in behavior regarding the occurrence of stereotypes, improved social contact, mood, sleep and appetite, which is why CBD was maintained.

Although patients in our sample used purified CBD extracts containing low doses of THC (<0.3%), as we progressed the dose of CBD, it is inevitable that these patients are proportionally exposed to a higher quantity of THC, which could explain worsening seizures during dose progression and return to the usual pattern at lower doses. Crippa et al (2016)[17] described two case reports of patients who used handcrafted products containing CBD extracts to treat epilepsy and initially evolved with symptom improvement, but later there was worsening of seizures associated with symptoms of THC intoxication (inap-

Table 1 General characteristics of the study patients

Age (years)	**Minimum: 1 year Maximum: 45 years**	**Average: 9.62**
Gender	Male Female	14 (58.3%) 10 (41.7%)
Epilepsy Type	Generalized Focal	17 (70.8%) 7 (29.2%)
Etiology of Epilepsy	Structural Genetic / Idiopathic	11 (45.8%) 13 (54.2%)
Epileptic syndromes	West syndrome Lennox-Gastaut Syndrome Dravet's Syndrome Doose Syndrome Landau-Kleffner Syndrome Nonspecific	4 (16.6%) 3 (12.5%) 2 (8.3%) 1 (4.2%) 1 (4.2%) 13 (54.2%)
Drugs before CBD	1 - 3 4 - 6 7 - 9	6 (25%) 8 (33.3%) 10 (41.7%)
CBD dose (mg / kg / day)	2.5 - 3.9 4 – 7.9 8 – 11.9 12 – 14	9 (37.5%) 10 (41.7%) 3 (12.5%) 2 (8.3%)
CBD Usage Time (months)	2-6 7-12 13-18 19-24 25-30 31-37	3 (12.5%) 6 (25%) 0 7 (29.2%) 5 (20.8%) 3 (12.5%)

Table 2 Response to CBD use according to type of epilepsy and epileptic syndrome (n = 24).

Response to CBD	% seizure reduction	n	% cases	Genetic etiology	Structural etiology	Epileptic syndrome
Seizure free	100%	4	16.6%	3	1	West (n=2) Generalized (n=2)
Marked response	80-99%	10	41.6%	5	5	West (n=2) Lennox(n=2) Dravet (n=1) Landau (n=1) Focal (n=2) Generalized (n=2)
Moderate response	50-79%	5	20.8%	4	1	Dravet (n=1) Generalized (n=2) Focal (n=2)
Little or No response	< 25%	1	4.2%		1	Lennox (n=1)
Worsening seizure pattern	Worsening	4	16.6%	1	3	Doose (n=1) Focal (n=3)

Table 3 CBD response in patients with defined epileptic syndrome (n = 11)

Epileptic syndrome	n	Response to CBD use
West syndrome	4	2 cases with complete seizure resolution 2 cases with 80-99% seizure reduction
Lennox-Gastaut Syndrome	3	2 cases with 80-99% seizure reduction 1 case with little or no answer
Dravet's Syndrome	2	1 case with 80-99% seizure reduction 1 case with 50-79% seizure reduction
Landau-Kleffner Syndrome	1	1 case with 80-99% seizure reduction
Doose Syndrome	1	1 case with seizure worsening

Table 4 Adverse effects documented in patients using CBD

Adverse effect	n	%
None	17	70.8%
Abdominal pain	4	16.6%
Drowsiness	3	12.5%
Weight gain	3	12.5%
Constipation	2	8.3%
Inappetence	2	8.3%
Insomnia	2	8.3%
Sialorrhea	1	4.2%
Valproate poisoning	1	4.2%
Status Epilepticus	1	4.2%

propriate laughter, ataxia, reduced attention and redness of the eye) which required replacement with the same dose of purified CBD, with improvement of intoxication symptoms and seizure remission. For this reason, there are questions within the medical literature about the potential toxicity of CBD formulations containing THC[6,10,17,20], not only regarding the psychoactive effects, but also for the potential for seizure exacerbation, especially in those patients who require high doses of CBD in their treatment. Regarding the adverse effects related to possible drug interactions between CBD and other antiepileptic drugs, in fact, one patient during the gradual increase of CBD dose showed signs of valproate intoxication (tremor and ataxia), confirmed by its elevated serum levels. These symptoms disappeared with decreasing valproate dose without changing the dosage of CBD. Although studies on drug interaction between CBD and valproate report an increased risk of elevated liver transaminases in this association[9], without directly influencing serum valproate levels, this finding was not what we found in our patients. Regarding the interaction of clobazam with CBD and the occurrence of drowsiness attributed to the accumulation of the metabolite desmethylclobazam[8], it was not possible, in our study, to monitor the serum levels of these drugs. However, of the three patients in our series who complained of drowsiness as a side effect, only one case was using clobazam concomitantly.

It is noteworthy that 17 patients (70.8%) denied any side effects with the use of CBD. Adverse effects observed in our sample such as abdominal pain, drowsiness, weight gain, constipation, poor appetite, insomnia and sialorrhea were, in general, well tolerated. Table 4.

We observed that, in addition to the anticonvulsant effect, parents reported other benefits. These findings were also observed at medical appointments, evolutionary neurological examination, and documented footage before and after CBD use in some cases. Although patients were not evaluated with neuropsychological testing, the main positive aspects reported were cognitive improvement, improved eye contact, social interaction, sustained attention, mood, sleep pattern, and autistic symptoms such as self-harm, heteroaggression and stereotypes. These results are consistent with several studies regarding the anti-inflammatory, antipsychotic and anxiolytic properties of CBD, and we find them to be as important as reducing seizures within patients' quality of life and health.

Our study has some methodological limitations, such as the relatively small sample size, no control group, data regarding the number and type of seizures were collected based on medical records or parental reports, without confirmation by video EEG. Variables inherent in the use of different brands of compounds containing CBD may also have influenced the results. Another limitation of our study is the fact that it is a retrospective study with a heterogeneous group of patients with various epileptic syndromes with different etiologies.

However, the results are in accordance with the findings described in the literature[7,11,12,13,15,16], which indicate positive therapeutic effects of CBD among patients with refractory epilepsy, promoting better quality of life without presenting significant adverse effects.

Conclusion

Faced with a frustrating scenario for the families of patients with drug-refractory epilepsy, without any quality of life and risk of sudden death, compounds containing CBD may be an adjunctive therapeutic option. It represents a promising alternative for epilepsy patients who do not respond to the conventional treatments available. Despite the limited sample of this study, most patients had seizure's frequency e intensity reduction. We observed satisfactory results regarding epileptic seizure control.

As for the occurrence of adverse events, CBD has proved to be a safe treatment option with a relatively mild side effect profile and good tolerability.

We have also found other benefits from CBD treatment, such as improved contact with the environment, cognition, language, social interaction, mood, and even improved motor development. Although our sample was quite heterogeneous, the results with better seizure control were patients with specific epileptic syndromes such as West Syndrome, Lennox Gastaut Syndrome and Dravet Syndrome.

It is still necessary to establish the ideal dose for treatment, since similar results are achieved with different doses used by different authors. In our experience, the results had similar efficacy to that reported by other authors using, on average, smaller doses of CBD.

Over the past five years, some clinical trials have noted CBD's efficacy in Dravet's Syndrome and Lennox Gastaut's Syndrome,

increasing the possibility of treatment in patients included in a group of highly refractory epilepsies with a consequent high occurrence of cognitive sequelae. However, well-designed clinical trials using CBD are needed to evaluate the efficacy of this drug in specific types of epilepsy, especially in younger patients (less than one year old) and among children with West syndrome. Limited data suggest CBD may be effective for treatment of refractory infantile spasms. Hussain (2020) conducted a study using synthetic CBD in a group of 9 infants with infantile spasms (refractory to treatment with hormone therapy and vigabatrin) and one child had satisfactory response of spasms control with treatment with CBD. [18] There is a growing interest of the medical community in conducting clinical trials involving CBD, including comparing the efficiency between synthetic formulations and the formulations extracted from the plant for refractory epilepsy, showing equal efficacy.[19]

However, only within the last two years that Class I evidence has been available for a pure form of CBD, based on placebo-controlled randomized clinical trials for patients with Lennox-Gastaut syndrome and Dravet syndrome. Arzimanoglou and collaborators in 2020 published a review article to provide information to neurologists and epileptologists on the therapeutic value of CBD products, principally a purified form, in routine practice for patients with intractable epilepsy.[20]

Studies involving the interaction of CBD with traditional and new antiepileptic drugs are scarce in the medical literature, as well as studies evaluating the effectiveness of CBD associated with ketogenic diet and treatment of Status epilepticus. Studies investigating these notes could help the physician to properly select the patient profile that would best respond to CBD .

Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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