

The impact of cannabidiol on epileptic children's quality of life

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Abstract

Objective: This study evaluates the impact of Cannabidiol on the quality of life of children followed at an outpatient ward in the city of João Pessoa after failed attempts at therapy with other antiepileptic medications. **Methodology:** This is a descriptive, cross-sectional, epidemiological study. This study has the home scenario, for convenience, with the application of a questionnaire to a group of parents or legal guardians of the epileptic children using cannabidiol oil, on the perceptions about the quality of life of the children. Our sample had 23 individuals. The population was made up of parents or legal guardians of children up to 17 years of age using cannabidiol-rich oil. A validated form developed by Mark Sabaz et al, entitled "Quality of Life in Childhood Epilepsy - Questionnaire QOLCE: Parent Form" was used. **Results and Discussion:** In Well Being, the mean score was 92.21 before CBD, and 76.95 after its use. In the Behavior section, the mean was 102.34 before CBD, and 67.34 after. In Health, the mean before CBD was 4.43, with a good evolution to 2.30 after its use. The mean Quality of Life described before cannabidiol was 4.65, also evolving to 2.34 after use of the substance. In Cognition an average of 79.65 was found before CBD and 101.26 after its use. The results confirm the hypothesis about the benefits of CBD on children's quality of life, and are mostly confluent with the literature on this topic.

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INTRODUCTION

The concept of epilepsy

Epilepsy is a disease usually diagnosed in childhood, difficult to control and chronic in nature. It is characterized by a persistent brain disorder, which generates exacerbated transient discharges in hyperexcitable neurons, causing epileptic seizures, which concern motor and sensory symptoms¹.

The diagnosis is essential to start monitoring and controlling the frequency of spells. Epilepsy is characterized as at least two unprovoked seizures within an interval of more than 24 hours, since within the space of one day it can be considered a single seizure without adequate resolution².

Cerebral involvement can be focal or diffuse, with different prognoses. The duration of the discharges is also an important analysis factor regarding disease severity, since excessive and repetitive electrical stimulation can cause permanent brain damage, associated with possible learning and even motor deficits. The spells that persist for more than 30 minutes is considered Status Epilepticus, a neurological emergency with a high risk of damage to the neuronal tissue, so it must be reversed immediately. Currently, the literature discusses the possibility of reducing this time to 5 minutes, aiming to initiate intensive therapy to stop the spell and avoid major and irreversible sequelae, with barbiturate coma being a last attempt at interruption³.

The relevance of drug therapy in the control of epileptic seizures

The importance of treating this condition lies in the knowledge that intellectual development takes place in childhood with greater intensity and speed, advances in organic systems, as well as in the individual's psychosocial traits. Convulsive spells can cause irreversible damage to brain tissue and cause psychological problems in children, who understand that they are different from others due to the typical characteristics of the disease. Children with epilepsy are more likely to develop behavioral, mental and learning disorders, emphasizing the need for effective control to prevent epileptic seizures. All these existing deficits in the natural development of the disease and in the currently recommended therapy generate a considerable drop in the quality of life of children⁴.

According to Eliana Garzon (2002), within the various etiologies of epilepsy, about 35% to 75% of patients continue to have epileptic seizures, even with adequate therapy. In the world, 50 million patients are diagnosed with the disease, but only 25% to 45% are stabilized, without spells recurrence for 1 year. The risk that difficult-to-control patients present is in the severity of the manifestations they may present. Uncontrolled episodes can develop into Status Epilepticus, and permanent brain damage can occur.

Effects of polydrug treatments in refractory epilepsies

A multidrug therapy is common in epileptic children due to the serious repercussions caused. Monotherapy is given at the initial diagnosis and should be kept escalated up to the maximum dose of the medication. In case of refractoriness of the spells, a drug with multiple mechanisms of action is associated. Therapy for epilepsy can be done with the association of up to 3 drugs in their maximum doses. The child who needs to undergo drug therapy for a long period of time (2 years being the interval conventionally adopted in cases with therapeutic success), is more easily exposed to drug interaction events. In addition, the drugs used to control the disease have different side effects, from nausea to important hepatotoxicity⁵.

Studies indicate that the probability of having a complete cessation of seizures after the use of 2 to 3 antiepileptic drugs (AEDs) is 5% to 10%. The medication is considered ineffective when symptoms persist even after dose optimization. There are studies that already conclude that in the case of monotherapy being ineffective, only 11% of the patients had an adequate response to polypharmacy treatment⁶.

Children are psychologically and socially disadvantaged by having to deal with the imprecise everyday life of the disease, and often develop behavioral and learning disorders. In addition to this perspective, treatment with polypharmacy is expensive and causes financial burdens for families. Spending on AEDs does not always return the response to treatment and there is still a need for multidisciplinary monitoring, requiring the approach of psychologists, physiotherapists, occupational therapists and other healthcare professionals.

Antiepileptic drugs as fundamental therapy and their adverse effects

Each antiepileptic medication has a more appropriate use, and its correct selection decreases the rates of adverse effects and drug interactions. Ataxia and dizziness are the most common damage caused by carbamazepine, phenytoin and phenobarbital, which are the three most used drugs. Among the variety of antiepileptic drugs, patients may still have diplopia, vertigo, allergies, weight gain, hirsutism, leukopenia and tremor. Valproate can cause hepatotoxicity. These drugs have a high rate of drug interaction with drugs common to everyday life, which when associated can cause osteopenia, hypercholesterolemia and increased cardiovascular risk. The adverse effects of these drugs worsen psychomotor, cognitive and, consequently, learning deficits that, generally speaking, epilepsy itself already causes. These data translate the idea that studies are needed in favor of a drug that can reduce these negative effects in the daily lives of patients diagnosed with epilepsy, who need the continuous use of drug therapy⁵.

Cannabidiol as a therapeutic option for refractory epilepsy

Currently, cannabidiol presents a scientifically proven alternative of effective action as AED. A study was carried out with 108 individuals in the pediatric age range who used CBD oil. The addition of CBD resulted in 39% of children having more than 50% seizure control, and 10% of them had complete remission of epileptic seizures. This analysis concluded that CBD brings efficacy to the treatment of epilepsy with the benefit of a low rate of significant adverse effects⁷.

Studies dating back to 1973, in Brazil, reveal the benefits of the drug to control crises refractory to multidrug therapy. Since 2014, there have been Brazilian requirements approved by ANVISA for the importation of Cannabidiol-based products. The Federal Board of Medicine, in the same year, authorized doctors to prescribe the substance as a treatment option for epileptic children with therapeutic failures. In December 2016, three families in Brazil obtained Court clearance for planting it for medicinal purposes. This scenario enabled, in 2017, the Associação Brasileira de Apoio Cannabis Esperança (ABRACE), in João Pessoa, to obtain authorization from the Federal Court of Paraíba to cultivate and manipulate marijuana for exclusively therapeutic purposes, enabling the treatment of more than 150 children with CBD⁸.

Matos et al⁸ (2017) reports that 40% of Cannabis sativa extracts are of the CBD component, with an antipsychotic and anxiolytic effect. The psychoactive effects are generated by the cannabidioid Delta-9-tetrahydrocannabinol (Δ^9 -THC), by stimulating the presynaptic efflux of dopamine in the prefrontal cortex, developing a state of euphoria. Its therapeutic use is aimed at improving appetite and weight gain in cancer patients or patients with serious debilitating illnesses. In contrast to Δ^9 -THC, CBD works as a competitive antagonist. It is the main non-psychoactive component of Cannabis sativa, and acts by inhibiting euphoria and a sense of humor⁸.

Based on scientific research worldwide, the hypothesis was formulated that the use of Cannabidiol in childhood Epilepsy brings a positive response in relation to the impact on the quality of life of children.

Therefore, the general objective of this study was to evaluate the impact of Cannabidiol on the quality of life of children monitored at an outpatient level in the city of João Pessoa, after failed attempts at therapy with other antiepileptic medications. This study aims to check follow-up data with children using oil rich in CBD, with the main purpose of clarifying the impact of this therapy on the quality of life of patients refractory to polypharmacy. The advancement of scientific research on the subject has a positive influence on facilitating patient access to treatment. João Pessoa is one of the rare centers of cultivation

of Cannabis Sativa; therefore, it presents good subsidies for carrying out data collection.

MATERIALS AND METHODS

Descriptive cross-sectional epidemiological study, based on a home scenario, with the application of a questionnaire to a group of parents or legal guardians of epileptic children using cannabidiol oil about their perceptions of their quality of life. This is a census survey that had a forecast of 30 individuals, but only 23 of the families agreed to participate. The population consisted of parents or legal guardians of children aged up to 17 years using cannabidiol-rich oil from 2013 to 2018. All parents or legal guardians of children with epilepsy refractory to the use of commonly prescribed medications were included in the study and started using cannabidiol-rich oil as the best option for controlling epileptic seizures between 2013 and 2018. Parents or legal guardians of children outside the predetermined age range and those who did not sign the consent form were excluded. An adapted validated form was used, prepared by Mark Sabaz et al⁹ (2003) entitled "Quality of Life in Childhood Epilepsy – Questionnaire QOLCE: Parent Form", which discusses physical activities, well-being, cognition, social activities, behavior, health and quality of life in children, and has no validation for the Portuguese language. The questionnaire was applied to the legal guardians so that they could answer about the data of 4 weeks prior to the use of the oil rich in CBD and another similar questionnaire to fill out about the last 4 weeks, after the use of the oil. The dependent variable used was the quality of life in patients using cannabidiol, and the independent variables were age group, sex, comorbidities and time of use of cannabidiol. Data were collected from interviews, systematized by dates, from February to April 2019. The questions were asked during a face-to-face interview, identified through a codename on an individual file, which was kept in a confidential envelope, which was only accessed again for data analysis. Data records were analyzed using contingency tables, aggregated before and after cannabidiol use. Data processing includes the description of the studied population's profile through simple and relative frequencies. It was stratified, considering the study variables. Comparisons were made between the groups before and after using the oil rich in CBD. A "p" value less than 0.05 was considered significant. For statistical analysis, we used the SPSS Statistics package. This study strictly considered the ethical norms in research involving human beings, according to Resolution No. 466/12 of the National Health Council, aiming to ensure the rights and duties that concern the scientific community vis-à-vis the research subjects. For this purpose, the permission of the legal guardian was requested through the informed consent form - TCLE, which was delivered beforehand, printed, for the participant to sign, authorizing the information previously provided for the research. The project

was approved by the Research Ethics Committee with CAAE 04388418.7.0000.5176.

RESULTS

Results were obtained from the characterization of 23 children with epilepsy, who use cannabidiol and are monitored in the city of João Pessoa, Paraíba. Seven children (30.4%) are female and 16 (68.6%) are male. Only parents of children in the pediatric age group were interviewed, and, at the time of the interview, 3 (13%) were between 0 and 5 years old, 12 (52.2%) were between 6 and 10 years old and 8 (34.8%) were between 11 and 17 years old. We found that 9 (39.1%) had comorbidities, all of which were neurological or psychiatric. Autistic Spectrum Disorder (ASD) was identified in 7 of these 9 and cerebral palsy in the other 2. The remaining 14 (60.9%) had no comorbidities.

Regarding the time of use of CBD, it was found that 9 (39.1%) of the children had been using it for up to 2 years, and 14 (60.9%) had been using it for more than 2 years, as shown in Table 1.

The parental form (QOLCE) was applied twice in each interview, one of which should be answered about prior to the use of cannabidiol and the other about the current situation, after the use. It is used based on the sum of the scores acquired in each variable evaluated. From these results, we were able to divide the variables into before and after. In the Well-Being, Behavior, Health and Quality of Life variables, the form has questions that should be answered from 1 to 6, and the lower the result, the better the child's situation is in the perception of the parents who are responding to the interview.

In the variables Cognition and Social Activity, also answered from 1 to 6, the questions are asked in such a way that the higher the result, the better the individual's situation according to the parents' perception.

In the Well-Being variable, the average score was 92.21 before using CBD, and 76.95 after using it, with a p -value <0.001 .

Continuing with the variables that assess improvement with decreasing scores, in the Behavior section, the average was 102.34 before CBD and 67.34 after, with a $p < 0.001$. The variable Health evaluates in an objective question, also scored from 1 to 6, the perception of parents or guardians about the general health of the child. In this sector, the average before CBD was 4.43, with a positive evolution to 2.30 after use, with $p < 0.001$. In the same way as the previous variable, Quality of Life was assessed by a single objective question about how parents perceived their respective children. The average described before cannabidiol was 4.65, also having an evolution to 2.34 after the use of the substance, with a p value <0.001 , as shown in Table 2.

The Social Activity section did not show a statistically significant " p " value. In addition to it, the Cognition variable also obtains a favorable result with the higher the score. It found an average of 79.65 before the use of CBD and 101.26 after its use, with $p < 0.001$, demonstrating a positive evolution in this study (Table 2).

DISCUSSION

The results show that there was a positive response in relation to the impact on the quality of life of children, through the studies carried out through the evaluation questionnaire (Quality of Life in Childhood Epilepsy Questionnaire QOLCE: Parent Form).

Talarska D.¹⁰ (2007) evaluated the functionality of the QOLCE to determine the quality of life of children with epilepsy. 160 children were monitored through clinical examinations and questionnaires filled out by parents and guardians. They concluded that the questionnaire is suitable for evaluating

Table 1. Characterization of the sample profile, João Pessoa - PB, 2019 (N=23).

	Frequency (n)	Percentage (%)
SEX		
Female	7	30.4
Male	16	68.6
AGE RANGE		
0 to 5 years	3	13
6 to 10 years	12	52.2
11 to 17 years	8	34.8
COMORBIDITIES		
Present	9	39.1
Absent	14	60.9
TIME USING CBD		
Up to 2 years	9	39.1
More than 2 years	14	60.9

Source: Author's Data, 2019

Table 2. Means and significance of the results from the QOLCE questionnaire before and after the use of CBD, João Pessoa - PB, 2019 (n=23).

	Minimum	Maximum	Mean	Standard deviation	p-value
WELL-BEING					<0.001
Before	65	105	92.21	9.53	
After	66	94	76.95	6.56	<0.001
COGNITION					
Before	59	117	79.65	17.16	
After	63	118	101.26	15.77	<0.85
SOCIAL ACTIVITY					
Before	25	45	36.60	5.34	
After	31	53	38.78	6.56	<0.001
BEHAVIOR					
Before	67	116	102.34	10.39	
After	43	112	67.34	19.44	
HEALTH					
Before	3	5	4.43	0.58	<0.001
After	1	4	2.30	0.76	
QUALITY OF LIFE					
Before	4	5	4.65	0.48	<0.001
After	1	4	2.34	0.77	

Source: Author's data, 2019.

children and adolescents, especially for cases refractory to medication, as happens with the children evaluated in this study.

Sonia Brucki et al.¹¹ (2015) demonstrated that there is a cognitive deficit in healthy patients who start using inhaled cannabidiol. In the same study, she exposes that CBD is not associated with progressive cognitive decline, but with a drop in performance at the time of inhalation. Different from the above, according to the data of this study based on the parents' perception expressed by the QOLCE, it is defined that there was an improvement in the children's cognitive performance.

Devinsky et al.¹² (2017) developed a double-blind study with CBD in children diagnosed with Dravet Syndrome, a neurological disorder characterized by intense epileptic seizures, drug resistance and high mortality. In it, they reported that 43% of the children using cannabidiol had a reduction of at least 50% of seizures, compared to the placebo group, which showed a reduction of 27%. Still among them, 5% of the patients were completely free of seizures in the group using CBD, but none achieved this result in the placebo group. According to Devinsky, the decrease in the frequency of seizures is directly intertwined with the improvement in patients' cognition and quality of life. Since the starting point for this present study is formed by children who already presented cognitive impairment in their underlying pathologies, it is justifiable that there is an improvement in the perception of this neurological function with the introduction of the drug, as was proven in the results with an evolution from an average of 79.65 before CBD to 101.26 after the introduction of CBD.

A study by Rosenberg et al.¹³ (2017) used the QOLCE to analyze the use of cannabidiol by patients for 12 weeks.

The results showed an evolution in Well-Being, especially in questions related to energy and fatigue. Cognition, in contrast to the study by Sonia Brucki et al.¹⁴, was presented as one of the factors that showed beneficial development after CBD. In view of the above, we acquired yet another reference that highlights the discrepancy between the assessment of cognitive progression in healthy patients and patients with neurological syndromes. In addition to these sections, the study by Rosenberg et al.¹³ also showed positive results on cannabidiol in the Social Activities and Behavior variables, the latter corroborating the results found in the present study, in which there was an important improvement in the behavioral section.

The Health and Quality of Life sections are determined by a single objective question in each of them, about the opinion of parents or guardians about the development of these areas before and after the drug. In both variables there was a 50% reduction in value, demonstrating that from the caregivers' point of view there is a significant improvement in the children's quality of life and in their health in general.

There was a limitation in the execution of the study, which concerned the scarce existence of literature about the evaluation, with the QOLCE, of children using cannabidiol. Therefore, the data presented in this study are unprecedented and it was necessary to discuss several variables that are not precisely identical to those found in the form used.

Due to the above, it was possible to observe the activity and influence of the use of cannabidiol to control epileptic seizures, providing an improvement in the quality of life of these children.

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