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Prospective evaluation of oral cannabis extracts in children with epilepsy

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ABSTRACT

Purpose: Interest in the use of artisanal cannabinoids in pediatric epilepsy has increased but safety and utility data are lacking. Our aim was to prospectively characterize the use of oral cannabis extracts (OCE) in a refractory pediatric epilepsy population.

Methods: Families considering the use of an OCE were enrolled in a prospective observational study. Baseline seizure frequency was assessed over a period of 4 weeks. Seizure frequency, CBD and THC-COOH levels were assessed every 4 weeks during a 12-week treatment period. Response was defined as at least a 50% reduction in seizure frequency over the final 8 weeks of the study relative to baseline.

Results: Consent was obtained in 32 children; 11 were excluded from analysis (3 failed to complete baseline data, 3 started OCE before completing baseline period and 5 did not start OCE) leaving 21 to be included in subsequent analyses. Median age was 10.3 years (IQR 6.8–12.6), 13 (62%) were male and median seizure frequency was 2.7 seizures/day during the baseline period. The median of the high dose of CBD that was administered during the observation period was of 0.9 (0.6–2.2) mg/kg/day. Of the 21 subjects who were included in the analysis, 5 (24%) were responders. OCE was stopped early in 3 subjects (14%) due to a perceived increase in seizures. THC-COOH and CBD blood levels did not have a significant association with response status ($p = 0.95$ CBD, $p = 0.53$ THC-COOH, $N = 14$).

Conclusion: The observed response rate in this study is similar to placebo rates in prospective randomized trials of pharmaceutical grade products and the withdrawal rate is greater than rates obtained with retrospective methods. Doses of OCE administered were lower than doses used in randomized trials.

1. Introduction

Interest in cannabis as a treatment for people living with epilepsy has increased over the last several years. The use of cannabis for epilepsy has been described in anecdotal reports for centuries [1–3]. Colorado voters passed a medicinal cannabis law allowing use for specific diagnoses in November 2000. Despite many new treatments becoming available in the last 20 years, including new antiseizure medications, neurostimulation, and improvements in surgical techniques and etiologic identification, many children living with epilepsy do not have well-controlled seizures [4–6]. The potential promise of cannabis has led to many families choosing this option before adequate studies can be completed.

Retrospective data suggest that some children with epilepsy have benefited from use of oral cannabis extracts (OCE). Surveys have found 84%–85% of families reporting a reduction of seizures with oral cannabis use with 14% reporting complete seizure freedom [7,8]. Retrospective chart reviews have found 49%–57% reporting some improvement, and 24–33% with a 50% reduction in seizures [9,10]. Additionally, in these studies, duration of treatment with OCE was around one year, with perceived benefit associated with longer use. Additionally, 30% of the group without perceived benefit for seizure control continued use of their product for more than 1 year [9]. While much of the media coverage has surrounded use in Dravet syndrome, these limited reviews found better perceived response in children with Lennox-Gastaut syndrome. Furthermore, these compounds have not

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demonstrated consistency and the contents do not reliably match labeling [11] with the FDA sending several warning letters regarding this issue [12].

Prospective open label and randomized studies have been performed using cannabidiol (CBD) enriched products that were able to demonstrate content consistency to the FDA. An open label study in children with medically refractory epilepsy found a greater than 50% reduction in seizures in 39% of patients, though adverse events were reported in the majority [13]. Randomized studies (blinded and placebo controlled) demonstrated statistically significant decreases in median seizure frequency between treatment and control groups. However, the proportion of patients experiencing at least a 50% reduction in seizures was significantly different between treatment groups in Lennox-Gastaut Syndrome, but not in Dravet Syndrome [14,15]. This formulation was recently approved by the FDA.

Many families have chosen to use OCE without data supporting efficacy or potential adverse events. In addition, some families have chosen to use THC products, either alone or in combination with CBD, for seizure control with very limited data. Our research proposed to follow children in a prospective manner when families chose to use OCE for treatment of refractory epilepsy to better characterize response rates, adverse events and types of products in use. Additionally, we attempted to capture other effects of OCE use, such as improvement in development and quality of life, that might lead to improvement in overall function but may not be reflected in seizure diary data.

2. Methods

Patients who were 1 month to 21 years of age, who were followed in the Children's Hospital Colorado pediatric neurology clinic and indicated they were planning to start a CBD product were approached for enrollment in the study. The children were required to have used two or more antiseizure medications, have at least 2 seizures per week, and maintain stable medication dosages for four weeks prior to enrollment. Subjects were required to keep stable dosing of antiseizure medications during the trial. Children with rapidly progressive epilepsy, treatable inborn errors of metabolism and current use of a medical marijuana product were excluded. Rapidly progressive epilepsy was defined as epilepsy that may not respond to anti-seizure medications due to the underlying etiology or may require other urgent treatment such as Rasmussen encephalitis. OCE products were purchased by families following state regulations and were not managed by providers in our clinic as none of the providers at our institution are registered prescribers for OCE. All families consented prior to participation based on IRB guidelines.

Seizure diaries were used to establish baseline seizure frequency over a four-week period prior to initiation of the OCE. Seizure type and frequency as well as use of rescue medications were documented on the paper seizure diary. A baseline EEG was performed to capture the sleep and wake states and labs were obtained prior to initiation of OCE, which was our recommended clinical protocol. Laboratory investigations included complete blood count (CBC), liver function testing (AST, ALT), and comprehensive metabolic panel, also recommended as part of our clinical protocol. Quantitative CBD, 7-CBD-COOH (a CBD metabolite) and THC-COOH levels were obtained as part of the study and assessed using a modification of an online extraction, high-performance liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS) method [16].

Children were followed for twelve weeks after initiation of OCE. Seizure diaries were maintained throughout the study and collected every four weeks. Labs were repeated every four weeks and EEG was repeated twelve weeks after initiation of OCE. Side effects were evaluated using the PESQ (Pediatric Epilepsy Side Effects Questionnaire) [17]. Development was assessed using the Scales of Independent Behavior, revised edition (SIB) [18] at baseline and at 12 weeks. Quality of life was measured using the Pediatric Quality of Life (PedsQL) [19] inventory at baseline and at 12 weeks.

Data was entered into a REDcap database [20] and analyzed using SAS 9.4. Additional data collected included age, epilepsy diagnosis, prior medications, current medications and seizure treatments. Demographic and clinical characteristics of the sample were presented as medians and interquartile ranges (continuous variables) or numbers and percentages (categorical variables). The outcome of interest was a dichotomous measure of response to OCE treatment, defined as a greater than 50% reduction in seizure frequency during the final eight-week period compared to baseline. Excluding the initial period of treatment allows for time to titrate OCE product, though there was not a true "maintenance period" and analysis of data reflects the time period after the introduction of OCE products. Seizure frequency was determined by total number of seizures during a time period divided by days in the period. In cases of missing seizure diary data, chart review was performed, with seizure response in these cases defined as documentation in the medical record of 50% percent or more reduction in seizures. EEGs were reviewed independently by KGK and KEC to determine subjective improvement such as reduction of seizures or improvement of interictal discharges compared to the individual's baseline EEG. Due to the variety of types of epilepsy, objective measures such as spike wave index and seizure counts could not be reasonably applied to all subjects. The results of the independent review for each subject were then compared to develop a consensus determination. Associations between demographic/clinical variables and responder status were assessed using a Wilcoxon rank-sum test (continuous) or Fisher's exact test (categorical). Scales for measuring impairment, side effects, and quality of life were compared at different time points using Wilcoxon signed-rank tests. Association between blood levels of CBD, 7-CBD-COOH and THC-COOH and administered dosages were assessed using a linear mixed-effects model with linear effect of dose concentration and a random intercept to account for within-patient correlation.

3. Results

There were 32 subjects enrolled in the study. Three subjects were not willing to collect baseline seizure data prior to starting an OCE, three failed to complete entry questionnaires and five never started an OCE; therefore, the final analysis included n = 21 subjects (Fig. 1). Median age was 10 years old. Patients had a median of 2.7 seizures per day and failed a median of 4 prior antiseizure medications (Table 1). Several epilepsy syndromes were represented, including Lennox-Gastaut Syndrome, Dravet syndrome, childhood absence epilepsy and focal

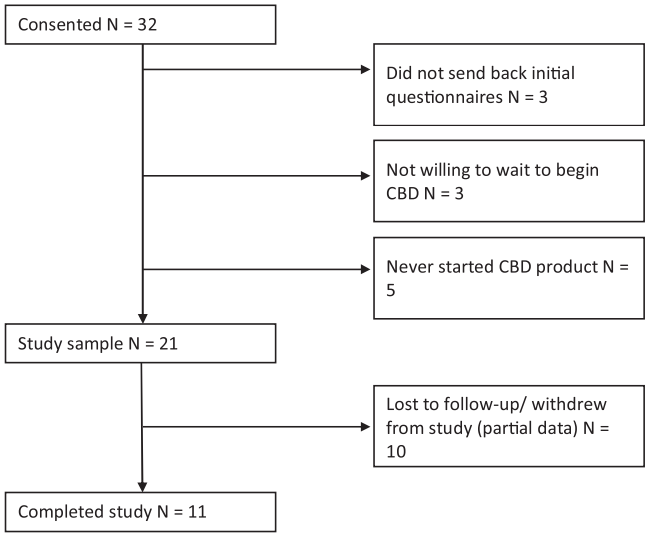

Fig. 1. Flow chart of participation eligibility and inclusion.

Table 1
Demographics by responder status.

	N(%) or median (IQR) n = 21	Non-responder N(%) or median (IQR) n = 16	Responder N(%) or median (IQR) n = 5	p-value
Age (years)	10.3 (6.8-12.6)	10.4 (7.4-13.0)	9.8 (2.0-10.4)	0.28
Time since seizure onset (years)	5.7 (3.4-9.6)	5.8 (3.7-10.1)	5.6 (1.6-9.1)	0.63
Prior failed medication trials (#)	4 (3-6)	4 (3-5.5)	5 (2-8)	0.70
Number of current meds	2 (1-3)	2 (1-3)	3 (2-5)	0.19
Number of seizure types	2 (1-4)	2.5 (1 -3.5)	2 (1-4)	0.83
Seizure frequency (per day)	2.7 (1.1-10.0)	2.7 (1.1-6.1)	11.8 (2.2-21.4)	0.31
Gender				
Male	61.9% (13)	68.8% (11)	40.0% (2)	0.33
Ethnicity/Race				
White/Caucasian	85.7% (18)	87.5% (14)	80.0% (4)	0.58
Hispanic	9.5% (2)	6.3% (1)	20.0% (1)	
Other	4.8% (1)	6.3% (1)		
VNS present				
Yes	14.3% (3)	12.5% (2)	20.0% (1)	> 0.99
Prior treatment with Ketogenic Diet/Modified Adkins Diet (MAD)				
Yes	42.9% (9)	43.8% (7)	40.0% (2)	> 0.99
Current Ketogenic Diet/MAD				
Yes	23.8% (5)	31.3% (5)	0.0% (0)	0.28
Prior OCE use				
Yes	5.9% (1)	8.3% (1)	0.0% (0)	> 0.99
Move to CO to access OCE				
Yes	28.6% (6)	12.5% (2)	80.0% (4)	0.01
Concurrent Clobazam Use				
Yes	47.6% (10)	50.0% (8)	40.0% (2)	> 0.99

Table 2
Epilepsy syndromes.

	N (%)
IGE (idiopathic generalized epilepsy)	3 (14.3%)
EE (epileptic encephalopathies)	14 (66.7%)
FE (focal epilepsy)	4 (19.0%)

epilepsy (Table 2).

The observed response rate was 24% (5/21). However, 14% (3/21) of patients stopped use of their product early due to an escalation of seizures. Two responders were identified using seizure diaries, while the remainder were determined by chart review. The exact seizure reduction was not calculated for subjects identified by chart review, but the two responders with completed seizure diaries both had an overall reduction in seizures of greater than 90%. EEG demonstrated an improvement in 2 of the 9 subjects that had both a baseline and follow up EEG. No demographic factors were found to be significantly associated with responder status with the exception of whether the participant had moved to Colorado to access OCE (p = 0.01) (Table 1).

At least nine different commercial products were used in varying concentrations; however, 52% of the subjects used the two most common products. The majority of subjects used a single product, though a sizeable minority (32%) used more than one product during the study period. Concentrations of all the products used were labeled for 9 subjects, whereas 8 subjects used products that did not have concentrations available and 4 used a combination of products that had labeled and unlabeled concentration. Over the course of this study, 16 subjects had CBD and THC-COOH levels obtained on at least one visit after baseline; of these subjects, 13 had detectable levels of THC-COOH and 15 had detectable levels of CBD, and 14 had detectable levels of 7-CBD-COOH. THC-COOH and 7-CBD-COOH levels were associated with the dose administered in those subjects where dosing was able to be determined though CBD levels were not (N = 27 observations on 13 subjects; p = 0.008, p = 0.0003 and p = 0.37 respectively). Average THC-COOH levels were higher in those who took only products with labeled concentrations compared with those who took unlabeled products (median (IQR) of 7.8 (0.9–9.1) vs 2.5 (0.0–10.6), but this difference was not statistically significant (p = 0.49). There was no difference in mean THC-COOH, 7-CBD-COOH or CBD serum levels between the responders and non-responders (p = 0.53, p = 0.82 and 0.95) (Table 3).

At baseline, nearly all subjects had minor abnormalities in blood counts and liver function, most of which consisted of mildly decreased white blood cell counts and mild elevations of liver enzymes; none of

Table 3
Subjects' use of cannabis products.

	N(%) or median (IQR)	Non-responder N(%) or median (IQR) n = 16	Responder study N(%) or median (IQR) n = 5	p-value
Subject's primary CBD product				0.81
Product A	33.3% (7)	37.5% (6)	20.0% (1)	
Product B	19.0% (4)	18.8% (3)	20.0% (1)	
Other/ unknown	47.6% (10)	43.8% (7)	60.0% (3)	
Initial dose (mg/kg)	0.6 (0.5-1.1)	0.9 (0.5-1.8)	0.6 (0.6-0.6)	0.39
Peak dose (mg/kg)	0.9 (0.6-2.2)	1.0 (0.3-2.7)	0.6 (0.6-1.0)	0.69
Subject used multiple products	31.6% (6)	21.4% (3)	60.0% (3)	0.26
THC-COOH detectable in blood samples	81.3% (13)	81.8% (9)	80.0% (4)	> 0.99
Mean THC-COOH level*	4.8 (0.9-9.8)	3.3 (0.9-8.2)	9.0 (0.8-12.7)	0.53
Mean CBD level*	3.1 (1.9-8.1)	2.9 (1.7-11.7)	3.4 (2.6-7.5)	0.95
Mean 7-CBD-COOH level*	88.4 (24.2-257.8)	105.9 (22.3-260.2)	69.0 (32.4-187.4)	0.82

* Undetectable values treated as 0.

these were clinically significant. These persisted throughout the study period, though two subjects had more significant elevations of liver function testing. All subjects were taking concurrent anti-seizure medications. Levels of desmethylclobazam increased in two of the three subjects for which this was measured, but this change was not statistically significant. Topiramate levels decreased in one of two subjects. Three children taking valproic acid saw a transient increase followed by a significant decrease in levels despite stable dosing.

SIB scores were obtained in 9 subjects at baseline and 12 weeks. Scores did not change during the duration of the study. PESQ was obtained at both 4 and 12 weeks in 6 subjects and there was no change in reported adverse effects during the time period of the study ($p = 0.56$). Similarly, there were no differences over time of PedsQL, including the total score ($p = 0.26$), psychosocial subscore ($p = 0.11$) or physical subscore ($p = 0.39$).

4. Discussion

This is the first reported prospective study to evaluate the use of artisanal oral cannabis extracts (OCE) in pediatric epilepsy in a real-world setting in a systematic manner. The overall response rate was similar to results of other retrospective studies of OCE and the rate of those stopping treatment was similar to prospective randomized trials of cannabidiol. Serum levels of CBD and THC-COOH were obtained but were not associated with response (reduction of seizures from baseline by 50%). Concentrations of THC-COOH and 7-CBD-COOH were associated with dosing whereas direct measurement of CBD was not, suggesting that these metabolites might be a more reliable measure. No family reported cessation of OCE due to side effects or safety concerns, other than lack of treatment response or an increase in seizures.

This observational study showed response rates similar to those found in prior retrospective data reported from our institution. Nearly a quarter of the subjects reported an improvement in seizure rates. Additionally, moving to Colorado to access an OCE was associated with a positive response, similar to prior retrospective studies.[9; 10] Comparing these rates to prospective studies evaluating CBD suggests that they are more similar to the placebo arms than treatment arms. In prospective studies, 43%–44% had at least a 50% reduction in seizures compared to 24%–27% of those in the placebo group.[14; 15] The absence of a placebo arm and lack of standardized dosing in our study make this difficult to decipher. Dosing in our observational data was lower (~1 mg/kg/day) than dosing that was used in randomized trials (5–20 mg/kg/day), raising the possibility of a dose-response effect.[14; 15]

Cessation of OCE products occurred at a similar rate compared to the treatment arms of the prospective randomized trials. Adverse events were not captured in a similar manner in our study, therefore direct comparison of adverse events is not possible. As a surrogate measure, 14% (3/21) of patients stopped use of their product secondary to adverse effects, all of which were due to an increase in seizures. Other studies reported 16% (14/86) stopped product in the LGS study due to side effects [14] and 15% (9/61) in the Dravet cohort [15]. No significant changes were noted using the PESQ, which was administered as a measure of side effects, suggesting that OCE were well tolerated. Most patients continued the OCE product despite a relatively low response rate of 24%. This is consistent with findings in prior work of long duration of use despite reporting no benefit in seizure control [9]. We attempted to address this by evaluating quality of life during the study; however, no difference was found compared to baseline. It is challenging to accurately know why families chose to continue OCE despite a lack of response.

Levels of CBD 7-CBD-COOH and THC-COOH did not correlate with reports of reduction of seizures, but doses used in our study were much lower than prior reports of CBD trials. Trials of cannabidiol in children with epilepsy that have demonstrated some efficacy have reported levels ranging from 200 to 600 ng/ml [21]. Doses of CBD used by families in this study were lower (~1 mg/kg/day) than the dosing that was used in the randomized trials, i.e., 20 mg/kg/day. Therefore, it is not surprising that levels were lower than in prior reports. Under-dosing is likely due to cost limitations since families paid for this treatment out of pocket. Correlation between serum levels and response have not yet been reported in prospective randomized trials. Another possibility is that the reported response in our cohort is not related to CBD or THC but could be related to another compound in the product. Families were accessing "whole plant" compounds, which are likely to contain a variety of chemical compounds. While THC-COOH levels did not correlate with response, there is little systematic clinical data on THC-COOH and seizures. A small prospective open-labeled study of a standardized CBD and THC containing product has demonstrated reduction of seizures in Dravet Syndrome [22]. There remain challenges in determining if a product containing THC and CBD may provide better seizure control and at what ratio, than CBD alone. Additionally, animal models of THC have not demonstrated consistent results. There was concern whether the OCE compounds contained CBD given FDA reports of products without detectable levels. Our subjects did have detectable CBD levels, supporting that the products contained at least some CBD. If OCE continues to be available for medical use, we recommend greater government oversight of product labeling and accuracy.

There were several limitations to our study. First and foremost, this was an observational study that did not include randomization or a placebo arm, limiting the interpretation of our results. Enrollment was low and some subjects were lost to follow-up or withdrew from the study prior to completion. This likely creates some bias in the sample, in our experience losses to follow-up are more likely among patients whose response to treatment is poor. The small sample size also limits the power and generalizability of the statistical analysis results. There was great variation in the products that were used by subjects in the study. In addition, the consistency of individual products was not demonstrated prior to this study, therefore the accuracy of reported dosages is likely low. Compliance with seizure diaries was lower than desired; therefore, chart review was required to determine responder rate in some subjects, Accuracy of data obtained via chart review was unclear in the absence of seizure diaries and often did not included seizure frequency limiting our ability to quantify change in seizure frequency in a more detailed fashion. Despite these limitations, the 'real world' aspects of this study design are likely useful to clinicians whose patients are using these products regularly.

5. Conclusion

Our results suggest that OCE may have some perceived benefit in this open-label prospective study, consistent with findings of retrospective studies of OCE, but not approaching the rates that were found in prospective randomized studies. Additionally, cessation rate of products due to side effects was similar to randomized prospective studies. This suggests that while there may be some response to artisanal OCE products, the risk-benefit ratio may not be as favorable as pharmaceutical-grade cannabidiol. Given the cost of pharmaceutical grade cannabidiol and limited indications to Dravet and Lennox-Gastaut syndrome, it is likely that the use of OCE will continue in children with other epilepsies. This study helps to characterize the use of OCE for the treatment of epilepsy in one of the early states to adopt its use but does not replace the need for randomized trials to determine efficacy. More states have legalized these products, therefore OCE use is likely to persist supporting that further studies are required and randomized placebo-controlled trials using OCE would be most helpful. Studies evaluating higher THC content products, that some families are using for treatment of epilepsy, seems especially prudent.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent

with those guidelines.

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Declaration of Competing Interest

KGK who has received research funding from Zogenix, Inc and West pharmaceuticals as well as consulting fees from Zogenix, Inc and Greenwich pharmaceuticals (DSMB member). The remaining authors have no conflicts of interest to report.

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