Vaporized cannabis for the acute treatment of migraine

A double-blind, placebo-controlled, crossover RCT

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INTRODUCTION

- Migraine is among the most common uses of cannabinoids for medicinal purposes.
- In a cross-sectional survey of 1,429 medical cannabis users, 35.5% of responders reported using medical cannabis for headache/migraine.
- In this survey, 81.4% of medical cannabis users employed inhalation as the most common method of administration.
- Patients ask healthcare professionals about cannabinoids; however, there is a paucity of data to inform medical advice.
- While there are numerous lines on converging preclinical evidence as well as retrospective studies and surveys suggesting that cannabinoids may have anti-migraine benefit, data on the efficacy of any cannabinoids for the acute treatment of migraine are limited to retrospective and survey studies with observational, unblinded, and non-controlled designs.
- The efficacy of cannabis for acute treatment of migraine had not previously been studied in a randomized, controlled trial (RCT).

METHODS

- Randomized, double-blind, placebo-controlled, crossover trial
- Single-center, the University of California, San Diego (UCSD).
- Study was approved by the UCSD Office of Institutional Review Board Administration (IRB #181944).
- Protocol was prospectively registered at ClinicalTrials.gov (NCT04360044).

Study Drug

- Cannabis used in this study was from the National Institute on Drug Abuse (NIDA) Drug Supply Program (DSP) and consisted of 4 treatments administered to treat 4 separate migraine attacks. They were: 1) ~6% THC/~11% CBD; 2) ~6% THC; 3) ~11% CBD; and 4) Placebo.

Participants

Inclusion criteria were: ages 21-65; any sex or gender; with migraine according to the criteria of the International Classification of Headache Disorders, 3rd edition[11] (ICHD-3); with 2-23 headache days and 2-23 migraine days per month; able to provide informed consent and complete questionnaires in English; agree not to use cannabis outside of the study; agree not to use opioids or barbiturates; and agree not to drive a motor vehicle within 4 hours following use of cannabis. Exclusion criteria were: urine drug test positive for THC, barbiturates, opioids, oxycodone, or methadone at screening visit; pregnant; breastfeeding; prisoner; known cognitive impairment; institutionalized; current moderate-severe or severe depression; current or past history of bipolar depression, schizophrenia, or psychosis; current or past history of any substance use disorder at the discretion of the research team; active pulmonary disease, class IV heart failure, cirrhosis, or other severe medical illnesses at the discretion of the research team; and allergy to cannabis.

Participants agreed not to use any other acute migraine treatments prior to or during the first 2 hours after study drug administration.

Enrollment

Patients were recruited November 2020-November 2022 . A board-certified headache neurologist experienced in ICHD-3 criteria (NMS) confirmed eligibility of all participants.

After participants provided written informed consent, baseline characteristics were captured using REDCap[12]. Then the participants were trained in the Foltin Uniform Puff Procedure (FUPP), a validated cannabis vaporization procedure, and an interactive smartphone application was installed on participants' smartphones for electronic momentary assessment (EMA)[13].

Randomization

Patients were randomized to receive the 4 different treatments using 1:1:1:1 assignment.

Blinding

Patients, research coordinators, investigators, and statisticians were blinded until after the statistical analysis was completed. The four different cannabis treatments were prepared into identical Storz & Bickel Filling Set capsules by a research pharmacist and placed into identical, sealed bags. Based on the randomization key, labels stating the order in which the patient would use the four treatments to treat four separate attacks ("Migraine 1" through "Migraine 4") were affixed to the sealed bags. The key linking the treatments to their identifying number was stored on a password-protected computer available only to a research pharmacist not otherwise involved in the study.

Patient blinding was promoted by using placebo cannabis from the NIDA DSP with identical taste to the other 3 treatments; by including a CBD arm, which does not have psychoactive effects; and by framing, including educating patients that they might experience a "high" from the CBD and placebo treatments and that they might not experience a "high" from the THC and THC/CBD mix treatments as the study dosages are lower than recreationally-used dosages .

Treatments

Upon migraine onset, the participant accessed the interactive smartphone application. The application would only allow the participant to proceed if it had been ≥7 days since the last cannabis administration, ensuring ≥7 days washout period between cannabis administrations. The application would also only permit the participant to proceed if it had been ≥2 days since the last reported headache, ensuring that participants were treating a new migraine attack and not a migraine recurrence. The application asked the participant questions to establish whether each migraine attack met criteria for treatment with study drug. These criteria were: 1) headache <4 hours from onset, 2) moderate or severe in intensity, 3) associated with photophobia and phonophobia or nausea, 4) no acute treatments used since onset of migraine. If the migraine attack met all criteria, then the application instructed the patient to vaporize study cannabis and provided the participant instructions for the FUPP to standardize vaporization procedure across treated migraine attacks and across participants. FUPP consists of five seconds of inhalation, followed by a ten second breath hold, exhalation, and 45 second waiting period before repeating the process. Participants were instructed to repeat the FUPP 4 times under the continuous guidance of the application. The application sent participants push notices at 1 hour, 2 hours, 24 hours and 48 hours to complete timed questionnaires to assess safety and efficacy outcomes.

Outcomes

The primary outcome was headache pain relief at 2 hours post-treatment. Co-secondary outcome measures were headache pain freedom at 2 hours and most bothersome symptom freedom (MBS) at 2 hours.

Analyses

The association of outcomes with four different treatments were assessed using a generalized linear mixed effects model. A random intercept structure was included to account for the cluster effect of subjects going through the same trial multiple times. We ignored the order of the treatment (session number) in this analysis. During the trials, some subjects filled out the survey before or after the expected timepoints. To minimize the loss of data due to the late/early responses, we performed a sensitivity analysis using a time window to retain as much subset of the data as possible without increasing possible exposure to retention bias. For the survey that was expected to be filled out at 2 hours after taking the treatment, only the responses that were made within 1.5 hours to 3 hours after taking the treatment were accepted. For trials with excluded survey response, the statistician checked the time when the previous or next survey were filed and used the previous or next survey response if those surveys were filled out at a reasonable time close to the 2 hours timepoint. Statistical analyses were performed using R Studio, version 4.1.2 (R Foundation for Statistical Computing). All tests were two-sided with $p<0.05$ indicating statistical significance. Binomial generalized mixed effects model with random intercept was used to calculate the p-values.

RESULTS

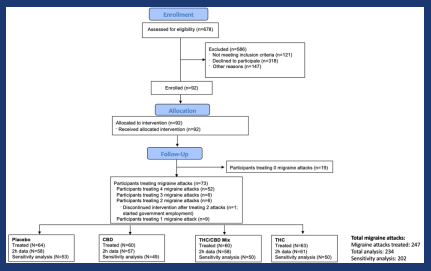

Figure 1: Enrollment, Randomization and Follow-up

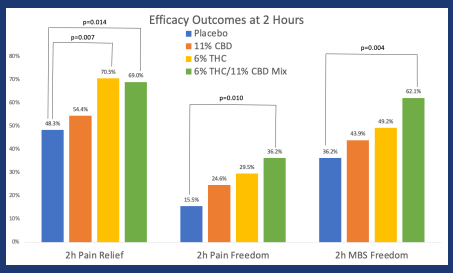

Figure 2: Efficacy Outcomes at 2 Hours for the Total Dataset (N=234)

Characteristic	All Patients (n=92)
Age- median years (Quartiles 1-3)	41 (34-54)
Sex- Male no. (%)	
Female	76 (82.6%)
Male	16 (17.4%)
Gender Identity-no. (%)	
Female sex	77 (83.7%)
Male sex	15 (16.3%)
BMI- median (Quartiles 1-3)	26.0 (22.8-32.9)
Ethnicity	
Hispanic or Latino	15 (16.3%)
Not Hispanic or Latino	77 (83.7%)
Race or ethnic group-no.(%)	
White	71 (77.2%)
Black	8 (8.9%)
Asian-American	7 (7.8%)
Mixed/Other	2 (2.2%)
Middle Eastern	1 (1.1%)
Pacific Islander	1 (1.1%)
Declined to state	2 (2.2%)
Primary language- no. (%)	
English	92 (90.1%)
Spanish	6 (6.6%)
Other	3 (3.3%)
Migraine history	
Age at onset- median years (Quartiles 1-3)	20 (14-28)
Headache Days per month- no.	15 (8-16)
Migraine Days per month- no.	6 (4-10)
Chronic Migraine*- no. (%)	25/91 (27.5%)
Most bothersome symptom, treated attack	
Photophobia	148 (63.2%)
Phonophobia	38 (16.2%)
Nausea	48 (20.5%)
Last Cannabis Use	
Never	33 (35.9%)
More than 1 year ago	19 (20.7%)
6 months-1 year ago	7 (7.6%)
1 month-6 months ago	19 (20.7%)
2 weeks-1 month ago	5 (5.4%)
Last 2 weeks	4 (4.3%)
Unknown- no. (%)	5 (5.4%)

Table 1: Baseline Characteristics of Patient Population

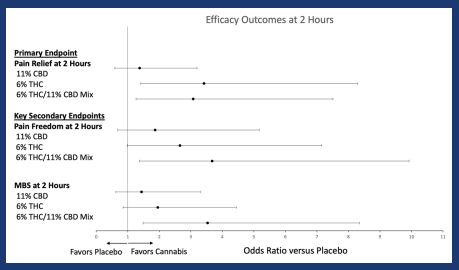

Figure 3: Forest plot of efficacy data at 2 hours for the total dataset (N=234)

678 people were screened for eligibility, of whom 92 were enrolled (Figure 1). Participants had a median age of 41, and 82.6% were female (Table 1).

247 migraine attacks from 73 participants were treated with vaporized cannabis; 60 migraine attacks were treated with THC/CBD, 63 migraine attacks were treated with THC, 60 migraine attacks were treated with CBD, and 64 migraine attacks were treated with placebo. Of these, 2 hour questionnaires were completed for 234 migraine attacks from 71 patients and were included in the total analysis; 58 migraine attacks treated with THC/CBD, 61 migraine attacks treated with THC, 57 migraine attacks treated with CBD, and 58 migraine attacks treated with placebo were included in the efficacy analysis. The sensitivity analysis included 202 migraine attacks from 70 patients who filled out timestamped 2-hour questionnaires between 1.5 hours and 3 hours; 50 migraine attacks treated with THC/CBD (86.2%), 50 migraine attacks treated with THC (82.0%), 49 migraine attacks treated with CBD (86.0%), and 53 migraine attacks treated with placebo (91.4%) were included in the efficacy analysis (Figure 1).

In the total dataset, the prespecified primary end point of pain relief at 2 hours was achieved by 67.2% with THC/CBD, 68.9% with THC, 52.6% with CBD, and 46.6% with placebo. The results were the same in the sensitivity analysis; 64.0% with THC/CBD, 70.0% with THC, 53.1% with CBD, and 45.3% with placebo. The differences were statistically significantly different between THC/CBD and placebo (p-value 0.016; OR 2.846, 95% CI 1.218-6.652) and between THC and placebo (p-value 0.008, OR 3.140, 95% 1.352,7.295). The key secondary endpoints of pain freedom at 2 hours and most bothersome symptom freedom at 2 hours were statistically significantly different between THC/CBD and placebo but not between THC and placebo or between CBD and placebo (Figures 2 and 3).

Sleepiness was the most common side effect, followed by euphoria. THC/CBD mix had lower rates of euphoria, cognitive impairment and subjective highness than THC dominant, but higher than CBD and placebo (Table 2). Across all 4 treatments there were no serious adverse events, emergency room presentations or need for acute interventions during the course of this study.

	Placebo	CBD	THC/CBD	THC
1 Hour (N)	N=60	N=56	N=56	N=58
Sleepiness	16 (26.7%)	21 (37.5%)	25 (44.6%)	24 (41.4%)
Euphoria	4 (7%)	5 (8.9%)	16 (28.6%)	21 (36.2%)
Cognitive Impairment	4 (7%)	8 (14.3%)	12 (21.4%)	20 (34.5%)
Highness (0-10) Mean (SD)	0.6 (1.2)	1.5 (2.0)	2.4 (2.5)	3.5 (3.0)
2 Hours (N)	N=58	N=57	N=58	N=61
Sleepiness	22 (37.9%)	29 (50.9%)	18 (31.0%)	26 (42.6%)
Euphoria	1 (1.7%)	2 (3.5%)	6 (10.3%)	17 (27.9%)
Cognitive Impairment	3 (5.2%)	4 (7.0%)	7 (12.1%)	17 (26.2%)
Highness (0-10) Mean (SD)	0.4 (1.0)	0.9 (1.6)	1.3 (1.9)	2.4 (2.8)

	Placebo	CBD	THC/CBD	THC
Participants reporting any adverse events	**3/60 (5.0%)**	**11/56 (19.6%)**	**11/56 (19.6%)**	**18/58 (31.0%)**
Adverse events reported by ≥1% of participants at 1 hour	**0**	**7**	**12**	**13**
Sedation	0	2	3	0
Slowness	0	1	0	4
Paresthesias	0	0	1	2
Throat irritation	0	3	2	0
Increased appetite	0	2	1	1
Impaired cognition	0	0	2	1
Very high	0	0	0	1
Impaired focus	0	0	2	2
Dizziness	0	0	0	2
Dry mouth	0	2	1	0
Adverse events reported by ≥1% of participants at 2 hours	**3/58 (5.2%)**	**4/57 (7.0%)**	**4/58 (6.9%)**	**11/61 (18.0%)**
Sedation	0	3	2	2
Impaired focus	1	0	0	1
Slowness	0	0	0	3
Dizziness	0	0	2	2
Throat irritation	0	1	1	0
Dry mouth	2	0	1	0
Paresthesias	0	0	0	1
Increased appetite	0	0	0	1
Impaired cognition	0	0	1	1
Very high	0	0	0	0
Serious adverse events	**0**	**0**	**0**	**0**

Tables 2 and 3: Adverse Events

CONCLUSIONS

- In this first randomized, double-blind, placebo-controlled trial testing the efficacy of cannabinoids for the acute treatment of migraine, 6% THC/11% CBD mix was superior to placebo for pain relief, pain freedom, and most bothersome symptom freedom at 2 hours.
- Questions remain warranting future research, such as long-term studies of the benefits and risks of repeated use.

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