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Original Research

Medical cannabis improved self-reported spasticity rating in patients with chronic spinal cord injury: a placebo-controlled, double-blind, crossover pilot clinical trial

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Abstract

Background: Previous studies demonstrated that cannabinoids may reduce spasticity in patients with spinal cord injury (SCI); however, the effect of naturally extracted THC:CBD oil, the most commonly used naturally extracted cannabinoids, has yet to be elucidated.

Objectives: To assess the effect of a 1:1 THC:CBD oil on reducing spasticity in chronic SCI patients

Design: A single-center, placebo-controlled, double-blind crossover clinical trial.

Methods: Sixteen chronic SCI patients with intractable spasticity were randomly assigned to either the intervention (1:1 THC:CBD oil) or control (placebo) phase for 1 month, then crossed over. The primary outcome (combined Ashworth Scale [AS] of all involved muscle groups) and the secondary outcomes, including patient-rated visual analog scale (VAS) of spasticity, were assessed before and after both phases and analyzed using a multilevel mixed-effects model.

Results: All participants completed the study. The average (SD) dose of THC:CBD oil was 11.6 (1.3) mg. No significant difference in the total AS score for all involved muscle groups was found between the pre- and post-treatment phases, or between the experimental and control phases (all $p > 0.05$). A significant reduction was observed in the patient rating VAS (effect size = −13.9 [95% CI: −25.5 to −2.3; $p = 0.010$).

Conclusion: In people with chronic SCI who had intractable spasticity, there was no statistically significant effect of 1:1 THC:CBD oil on spasticity-related outcomes, except for patient rating VAS reduction. Further studies are needed to evaluate the efficacy of higher doses of THC (>12 mg/day) and to use patient-reported spasticity scores as the primary outcome measure.

Trial registration: The study was registered with the Thai Clinical Trials Registry (TCTR identification number: TCTR20220329001).

Plain language summary

The effect of cannabis oil on reducing spasticity after spinal cord injury

Researchers wanted to test whether a cannabis oil containing equal parts THC and CBD could help reduce spasticity in people with long-term spinal cord injuries. Previous research suggested cannabinoids might help, but this specific type of natural oil had not been adequately tested yet. The study involved 16 patients with chronic spinal cord

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injuries who had severe, difficult-to-treat spasticity. In a carefully controlled experiment, each patient received either the THC:CBD oil or a placebo for one month, then switched to the other treatment for another month. Neither the patients nor the researchers knew which treatment was real during the study. The researchers measured spasticity using two methods: a clinical test performed by doctors and a patient's own pain rating scale. When physicians measured muscle stiffness using clinical tests, there was no meaningful difference between the THC:CBD oil and the placebo. However, patients who took the oil reported that their spasticity felt somewhat better compared to placebo, with an average improvement score of about 14 points on a 100-point spasticity scale. The average dose used was about 11.6 mg of the oil per day. The study suggests that this particular dose of THC:CBD oil may not significantly improve spasticity in the way doctors can objectively measure it. However, patients felt relief, which is important. The researchers note that higher doses might be more effective and recommend that future studies focus more on what patients themselves report rather than just on clinical measurements.

Keywords: cannabidiol, cannabinoids, spasticity, spinal cord injury, tetrahydrocannabinol

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Introduction

Spasticity is one of the most common secondary conditions following spinal cord injury (SCI), as 78% of people with chronic SCI reported spasticity problems.[1] In people with SCI where spasticity is involved in several muscle groups, the treatment of choice should focus on oral medications, including baclofen and tizanidine.[2] However, 41% of people with chronic SCI still reported intractable spasticity, indicated by persisting spasticity despite administering maximum dosage or inability to tolerate the adverse events of medications.[2] Intractable spasticity decreases function (e.g., ability to perform activities of daily living), creates difficulties for caregivers, and reduces the quality of life of people living with chronic SCI.[2] Therefore, studies aiming to explore novel antispastic medication as a treatment option for treating spasticity in people with SCI are needed.

Previous evidence demonstrated the use of cannabinoids for treating spasticity following SCI. For example, a study demonstrated that oral nabilone, which is a synthetic cannabinoid of Delta-9-tetrahydrocannabinol (THC), could significantly attenuate spasticity in people with chronic SCI.[3] Another study reported that dronabinol, a phytocannabinoid predominantly containing THC, could significantly reduce spasticity in people with chronic SCI.[4] However, these two studies similarly reported the incidence of serious adverse events, including increased pain, anxiety, decreased attention and mood, resulting in numerous drop-out participants. On the other hand, evidence demonstrating the effect of CBD on reducing spasticity is presented in patients with multiple sclerosis (MS).[5] Therefore, the medical cannabis treatment recommended in the UK and Europe for multiple sclerosis is Sativex®, which is a 1:1 CBD:THC oromucosal spray because CBD alone was found to be ineffective.[6,7] Compared with THC, CBD has lower psychoactive properties (not causing high emotion and not addictive) and may have additional beneficial effects such as improving mental health concerns and preventing oxidative damage, as well as preventing adverse events from THC.[8] Therefore, it should be hypothesized that the combined THC and CBD cannabinoids should reduce spasticity in those with SCI and cause low psychiatric adverse events, although evidence has yet to be explored.

As Sativex® has not been legally registered in Thailand, whereas cannabinoids are increasingly used for medical purposes after it has been medically legal in Thailand, the Government Pharmaceutical Organisation of Thailand then manufactured many forms of cannabinoid drugs,

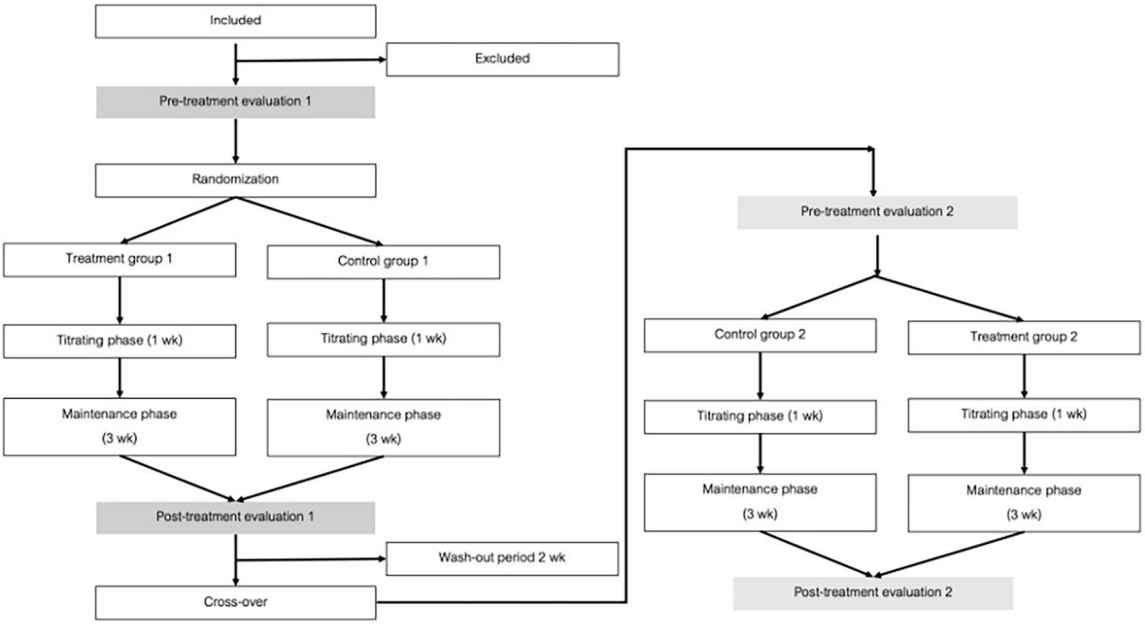

Figure 1. The summarized protocol.

including high THC, high cannabidiol (CBD), and 1:1 THC:CBD form. This study aimed to evaluate the effect of naturally extracted 1:1 THC:CBD oil on reducing spasticity in people with chronic SCI who have generalized refractory spasticity. We hypothesized that the naturally extracted 1:1 THC:CBD oil used in this study can reduce spasticity better than a placebo.

Methods

Study design

This study was a single-center, placebo-controlled, double-blind (patients, investigators–including treatment providers, assessors, and analyzers) crossover pilot clinical trial. We used the crossover design since it can equalize baseline characteristics and severity of spasticity between the comparison groups, thereby preventing the risk of selection bias. Each patient with SCI has differential characteristics that could potentially confound the treatment effect.[9] Also, the crossover design can reduce the sample size of the study as the SCI population is relatively rare, which affects the recruitment process. All research activities were conducted at the Department of Rehabilitation Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, from May 2022 to December 2024.

Ethical consideration and trial registration

The study was approved by the Ethical Committee of the Faculty of Medicine, Chiang Mai University, in compliance with the Declaration of Helsinki (Study ID: REH 2564 08541, obtained date 21 December 2021). The study was registered with the Thai Clinical Trials Registry (TCTR identification number: TCTR20220329001). All participants provided written informed consent to participate in this study and to publish results that include their deidentified data.

Study protocol

The summarized protocol is shown in Figure 1. After giving informed consent, 16 individuals with chronic SCI who have intractable spasticity were admitted. The participants were randomly assigned to either the intervention group or the control group. Participants would receive pre-treatment-1 evaluation for determining baseline characteristics and the severity of spasticity, including the sum AS of all affected muscle groups as a primary outcome. After the pre-treatment-1 evaluation, participants in the intervention group would receive the 1:1 THC:CBD oil, whereas the participants in the control group would receive the placebo, adding on to their current spasticity treatment, for 4 weeks (1 week for titration *plus* 3 weeks for maintenance). Then, participants would be

evaluated for a post-treatment-1 assessment. After that, the investigated drug was stopped for 2 weeks as a washout period. After finishing the washout period, participants were crossed over, that is, those who were in the intervention group in the first phase would be in the control group, and vice versa. Urine cannabinoids were evaluated to confirm that there was no carry-over effect. The participants were evaluated for the pre-treatment-2 assessment, which was similar to the pre-treatment-1 assessment. The second treatment period also consisted of 4 weeks. After completing the treatment protocol of 4 weeks, the post-treatment-2 assessment evaluation was conducted. Comparisons of outcomes between the two, that is, the intervention and control periods, were analyzed to determine the efficacy and safety of 1:1 THC:CBD oil using inferential statistics. The titration protocol and the safety control of this study were presented in Supplemental Data.

Randomization, allocation concealment, and blinding methods

Computer-generated simple randomization was used as a sequence generation method. Allocation concealment was performed using a password-secured randomization table and was only accessible to a research assistant who was not responsible for treatment administration, outcome assessment, and statistical analysis. The treatment allocation was blinded to the patients, investigators, assessors, and analyzers by limiting access to the allocation sequence and assignment.

Participants

The inclusion criteria of this study were: (1) being diagnosed with SCI from traumatic or degenerative spinal etiology with any level and severity of injury; (2) onset of injury more than or equal to 1 year; (3) age between 20 and 65 years; (4) having intractable systemic spasticity (AS $\geq$ 2 despite receiving maximum tolerable oral antispastic drugs). The full exclusion criteria are listed in the Supplemental Data, which include: (1) a history of having comorbidities (pregnancy and lactation, cardiovascular, neurological other than SCI, liver, kidney, and psychiatric diseases), laboratory results (AST or ALT $>$ 3 times than upper normal limits, creatinine clearance less than or equal to 20 mL/min, cytopenia) and currently using the medication that are potentially harmful for using cannabinoids, including carbamazepine, phenytoin, fluoxetine, valproic acid. Participants who currently use cannabinoids (positive urine cannabinoid screening test), have a history of allergy to cannabis or cannabinoids, or have a history of allergy to sesame, an ingredient of the oil, would be excluded.

Interventions and comparisons

The 1:1 THC:CBD oil used in this study was provided by the Government Pharmaceutical Organization of Thailand (GPO). Our THC:CBD oil was extracted using a cold extraction method with alcohol as the solvent to prevent a synergistic effect from other solvents, such as terpenes. This oil contains THC for 27 mg/ml or 1 mg/drop and CBD for 25 mg/ml or 1 mg/drop. The placebo was prepared by the GPO. It had a similar smell to the 1:1 THC:CBD oil without any active ingredient. As the study aims to assess the effect of 1:1 THC:CBD oil as an additional treatment for participants with intractable spasticity, there will be no adjustment to previously used antispastic drugs; that is, all participants will continue their spasticity medications throughout the trial without any adjustments. The names of all concomitant medications were collected. During each treatment period, participants would attend standard physical and occupational therapy for controlling spasticity, including a range of motion exercise, stretching exercise, and tilt table positioning, at least 1 h a day, 5 days a week.

Outcome assessment

All outcomes for all participants were assessed by SP and NB, who were trained with the same standard, and each participant was assessed by one assessor.

Ashworth scale

The primary outcome of this study is the summation of the Ashworth Scale (AS) of all affected muscle groups. The Ashworth Scale is the most common approach to evaluating the level of spasticity in research.[8] The scale grades resistance to rapid passive movement across a relaxed joint on an ordinal scale of: 0 (no increase in tone); 1 (slight increase in tone giving a catch when the limb is moved); 2 (more marked increase in tone, but limb easily flexed); 3 (considerable increase in

tone, passive movement difficult); and 4 (limb rigid in flexion or extension proposed).[10] Although the Modified Ashworth Scale (MAS), another version of the scale, is used clinically, it is not routinely used in research because there is a 1+ score, which prevents the summation.[11]

The summation of the AS was bilaterally assessed only in muscle groups that had spasticity (both upper and lower extremity muscles in tetraplegia and only lower extremity muscles in paraplegia).[4] Details of all muscle groups are presented in Supplemental Data.

Spasm frequency scale (SFS)

The SFS testing was conducted by asking subjects to complete the Spasm Frequency Index pre- and post-treatment. The scales include grade 0 (no spasm); grade 1 (1 spasm/day); grade 2 (2-5 spasms/day); grade 3 (6–9 spasms/day); and grade 4 (⩾10 spasms/day).[12]

Patient and physician rating VAS for spasticity

Spasticity was rated by the patient and physician using a visual analog scale of 0–100 (VAS 0-100).[4] These measurements provided patients and physicians with subjective dimensions of spasticity.

The amplitude of the H/M ratio from the H-reflex

Neuronal excitability by assessing the H/M ratio of amplitude during nerve conduction study, which was used as surrogate evidence according to the evidence that H-reflex will be reduced after baclofen treatment in MS patients.[10] H-reflex testing was performed using a modification of the technique described by Little and Halar[13] (Supplemental Data). The maximum H-reflex amplitude and M-response were recorded, then the H/M ratio was calculated.[10]

Safety outcomes

The overall, serious, and non-serious adverse events would be collected, and the incidence rate would be calculated in both per-group and per-individual fashion.

Sample size calculation

Since no study has demonstrated the effect of this drug, the sample size was estimated based on the effect size from a previous study with nabilone.[4]. The primary outcome of this study was the summation of AS after treatment; the sample size was calculated by using the formula for comparing the means of the outcome between the two groups. When applying a formula for calculating the sample size in a crossover study[14] and substituting the variables =0.05, =0.2, allowable difference = 2.55,[4], population variance = 1.525,4, and superiority margin = 2, the calculated sample size is 16.

Statistical analysis

All statistical analyses were performed using STATA version 17.0 (StataCorp, 2021. Stata Statistical Software: Release 18. College Station, TX, USA: StataCorp LP). All analyses were conducted using complete case analysis, that is, no imputation was performed. A one-tailed *p*-value was adjusted from the calculated two-tailed *p*-value from the previously described criteria.[15] A p-value of less than 0.05 was considered statistically significant. The magnitude of the effect size on the sum AS score was determined using Cohen's *d* (mean difference divided by pooled SD).[15]

For inferential analysis of spasticity outcome variables, differences within the group and between groups were compared using the Wilcoxon signed-rank test (crude differences) and multilevel mixed-effect model method with repeated measures (adjusted for differences in each patient) and adjusted for pre-treatment sum AS score. For inferential analysis of the categorical outcomes, that is, the adverse event incidence, the difference between groups was determined using the McNemar test for the level of statistical significance and risk ratio (RR) for direction and strength of the association.

Results

Participants recruitment

Figure 2 demonstrates a study flow according to the Consolidated Standards of Reporting Trials (CONSORT) diagram.[16] Sixteen participants (5% of patients in the database, 44% of the

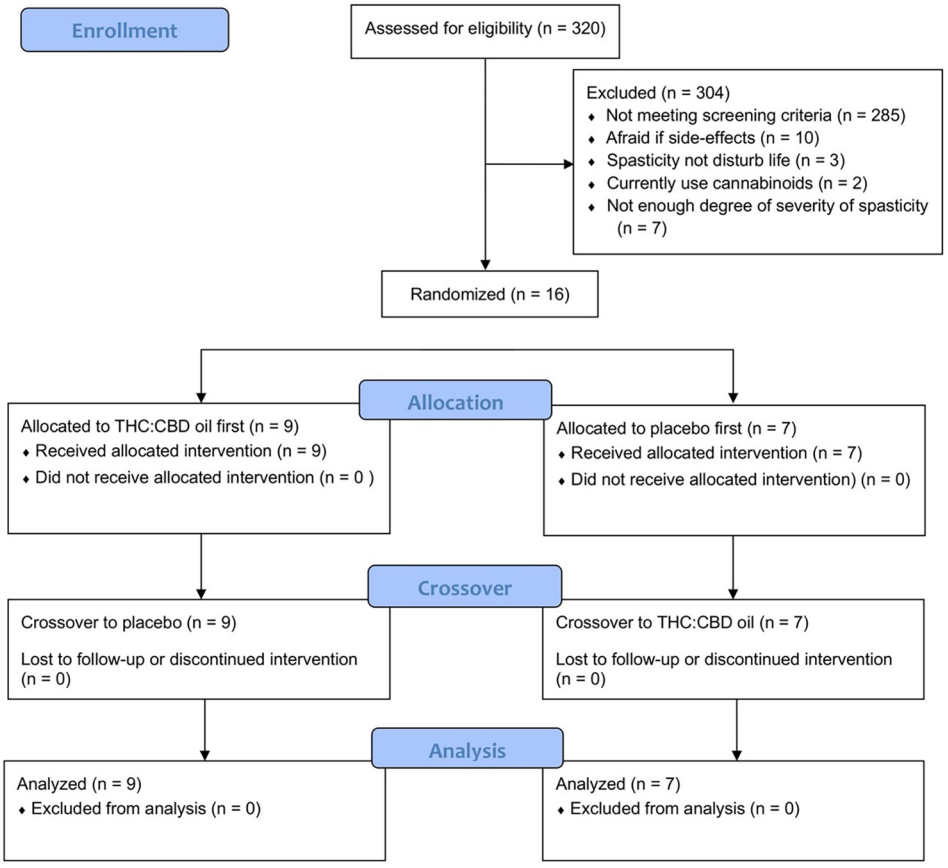

Figure 2. The Consolidated Standards of Reporting Trials (CONSORT) diagram.

contacted individuals, and 70% of the assessed individuals) were included in the study.

Baseline characteristics of the participants

Table 1 demonstrates the characteristics of all 16 participants. The mean (SD) age was 41.4 (12.0) years. Fifteen participants were male (94%). The mean (SD) time since SCI was 5.1 (5.1) years. Most participants lived with tetraplegia ($n = 10$, 62.5%) and had an incomplete SCI ($n = 9$, 56.2%). No participant had used cannabis or cannabinoid-containing substances before. All participants had received the maximal tolerable dosage of baclofen ($n = 16$, 100%) and tizanidine ($n = 13$, 81.3%) but still had intractable spasticity, indicated by having AS of the most affected muscle group of more than or equal to 2. According to the severity of spasticity, the mean (SD) initial AS of all affected muscle groups of the participants was 2.8 (0.7). Six participants had the maximum AS of 2, eight participants had the maximum AS of 3, and 2 participants had the maximum AS of 4. The mean (SD) summation of AS was 21 (8.8).

Feasibility of the protocol

All 16 participants completed the protocols of the intervention and control phase without withdrawal. The mean (SD) dosage of 1:1 THC:CBD oil used in the intervention group was 11.75 (1.0) per day. Fifteen participants received the maximum dosage of THC indicated in the protocol (12 mg/day), whereas one participant received the maximum dosage of THC at 8 mg/day, since the therapeutic effect ($AS < 2$) had been reached on that dosage. The protocol was delayed two times, both in the intervention phase, due to non-serious adverse events (one event of hypotension and one event of bradycardia).

Table 1. Baseline characteristics of the participants ($n = 16$).

Characteristics	Values
Age (year) [Mean (SD)]	41.4 (12.0)
Time since SCI (year) [Mean (SD)]	5.1 (5.1)
Time since SCI (year) [Median (25th, 75th percentile)]	2.0 (2.0, 9.0)
Sex [*n* (%)]	
Male	15 (93.7)
Female	1 (6.3)
Level of SCI [*n* (%)]	
Tetraplegia	10 (62.5)
Paraplegia	6 (37.5)
Completeness of SCI [*n* (%)]	
Complete	7 (43.8)
Incomplete	9 (56.2)
ASIA Impairment Scale (AIS) [*n* (%)]	
A	7 (43.8)
B	3 (19.8)
C	4 (25.0)
D	2 (13.4)
Medications [*n* (%)]	
Baclofen	16 (100.0)
Tizanidine	13 (81.0)
Others	0 (0.0)
History of using cannabinoids [n (%)]	
Yes	0 (0.0)
No	16 (100.0)
Initial spasticity parameters [Mean (SD)]	
Initial maximum AS	2.8 (0.7)
Initial summation of AS	21 (8.8)
Initial SFS	2.9 (0.8)
Initial Physician rating VAS	68.8 (18.3)
Initial Patient rating VAS	75.0 (18.6)
Initial H/M ratio (Rt) (%) ($n = 11$)	45.3 (22.8)
Initial H/M ratio (Lt) (%) ($n = 10$)	50.1 (23.1)

AS, Ashworth Scale; H/M, H-response per M-response ratio; SCI, spinal cord injury; SD, standard deviation; SFS, Spasm Frequency Scale; VAS, visual analog scale.

Table 2. Comparisons of safety profiles.

Overall adverse events	**THC:CBD**	**Placebo**	***p*-Value**	**Risk ratio [95% CI]**
Number of events	5	1	0.073	
Incidence per patients	31.25	6.25	0.060	5.00 [0.91–27.52]
Serious adverse events	**THC:CBD**	**Placebo**	***p*-value**	**Risk ratio [95% CI]**
Number of events	0	0	NA	
Incidence (%)	0	0	NA	NA
Non-serious adverse events	**THC:CBD**	**Placebo**	***p*-value**	**Risk ratio [95% CI]**
Number of events	5	1	0.073	
Incidence (%)	31.25	6.25	0.060	5.00 [0.91–27.52]

Significant level at $p < 0.05$ by the Wilcoxon signed-rank test for continuous or count data and McNemar test for categorical data.
CBD, cannabidiol; NA, not applicable; SD, standard deviation; THC, tetrahydrocannabinol.

Safety of the 1:1 THC:CBD oil

Table 2 demonstrates the safety of the 1:1 THC:CBD oil. There was no incidence of a severe adverse event in either study phase; therefore, no participant was withdrawn. There were five non-serious adverse events detected in five participants during the intervention phase but only one during the control phase, causing a non-significantly higher incidence of non-serious adverse events and overall adverse events in the intervention phase when compared with the control phase (5 vs 1, $p = 0.073$, McNemar test) with a risk ratio of 5.00 [95%CI: 0.91–27.52]. Five non-serious adverse events in the intervention phase included one symptomatic hypotension (BP=70/40), one asymptomatic bradycardia (HR = 56/min), and three events of non-significant hepatic enzyme elevation (2 times elevation of AST and ALT). Therefore, the incidence of non-serious, cardiovascular, and hepatic adverse events tended to be increased after use (incidence of 12.5% and 18.75%, respectively). One event in the control phase was non-significant hepatic enzyme elevation, which occurred during the titration phase. The symptomatic hypotension and symptomatic bradycardia events were treated by holding the dosage of the medication one step for 1 day and then returning to the titration protocol. Four events of hepatic enzyme elevation were treated by expectant management and resolved within 1-week of follow-up.

Efficacy of 1:1 THC:CBD oil on reducing spasticity

Table 3 demonstrates the efficacy of 1:1 THC:CBD oil in reducing spasticity from the crude analysis. Since this study used a crossover design, we first demonstrated a period effect and a sequence effect on the intervention. There was no statistically significant difference in the spasticity outcomes, including the sum AS, SFS, Physician rating VAS, Patient rating VAS, and percentage of tibial H:M ratio of the right and the left side, between two periods, that is, comparing between the first and the second period regardless of the intervention group (all $p > 0.05$, Wilcoxon signed-rank test). Also, there was no statistically significant difference in the intervention effect between the two sequences, that is, those who started with the intervention phase versus those who started with the control phase (all $p > 0.05$, Wilcoxon signed-rank test). Therefore, there was no significant period and sequence effect in this study, so direct comparisons between the intervention and control phase could be conducted.

Focusing on the primary outcome, that is, the sum AS, there was no statistically significant difference in the pre-to-post-treatment difference in sum AS between the intervention and the control phase [mean (SD) for intervention: −3.7 (7.0) vs mean (SD) for control: −5.4 (3.8), $p = 0.832$; Wilcoxon signed-rank test] (Figure 3). Notably,

Table 3. Comparisons of efficacy on reducing spasticity from the crude analysis.

Parameters	Pre THC:CBD, mean (SD)	Post THC:CBD, mean (SD)	THC:CBD post-pre, mean (SD)	Pre placebo, mean (SD)	Post placebo, mean (SD)	Placebo post-pre, mean (SD)	THC:CBD-placebo difference in post-pre, mean (95% CI; effect size)	*p*-Value (Wilcoxon signed-rank test; (one-tail)	*p*-Value of period (Period effect; Wilcoxon signed-rank test)	*p*-Value of intervention if sequence = ½ (Sequence effect; Wilcoxon signed-rank test)
Summation of AS	20.5 (9.0)	16.8 (7.8)	−3.7 (7.0)	20.0 (7.1)	14.6 (6.0)	−5.4 (3.8)	1.7 [−0.6 to 4.0]	0.832	0.416	0.287/0.650
SFS	2.6 (1.0)	2.6 (1.2)	−0.1 (0.4)	2.6 (1.0)	2.4 (1.0)	−0.1 (0.3)	0.1 [−0.1 to 0.3]	0.673	0.179	0.330/0.248
Physician rating VAS	61.0 (20.2)	47.3 (23.7)	−13.7 (18.8)	67.2 (20.7)	46.9 (17.3)	−20.3 (20.5)	6.6 [−3.1 to 16.3]	0.888	0.879	0.375/0.75
Patient rating VAS	70.0 (20.0)	57.5 (16.9)	−12.5 (11.3)	68.1 (21.0)	49.4 (12.4)	−18.8 (24.2)	6.3 [−1.8 to 14.4]	0.846	0.969	0.559/0.642
H:M ratio Rt (%)	35.6 (15.3)	30.8 (17.7)	−4.8 (18.2)	55.4 (25.9)	38.1 (23.1)	−17.3 (28.5)	12.5 [−0.1 to 25.1]	0.885	0.576	0.337/0.602
H:M ratio Lt (%)	46.5 (23.1)	43.9 (26.0)	−2.6 (17.8)	52.7 (18.5)	44.6 (26.0)	−8.1 (26.6)	5.5 [−5.4 to 16.4]	0.822	0.597	0.917/0.465

AS, Ashworth Scale; CBD, cannabidiol; H/M, H-response per M-response ratio; SD, standard deviation; SFS, Spasm Frequency Scale; THC, tetrahydrocannabinol; VAS, visual analog scale.

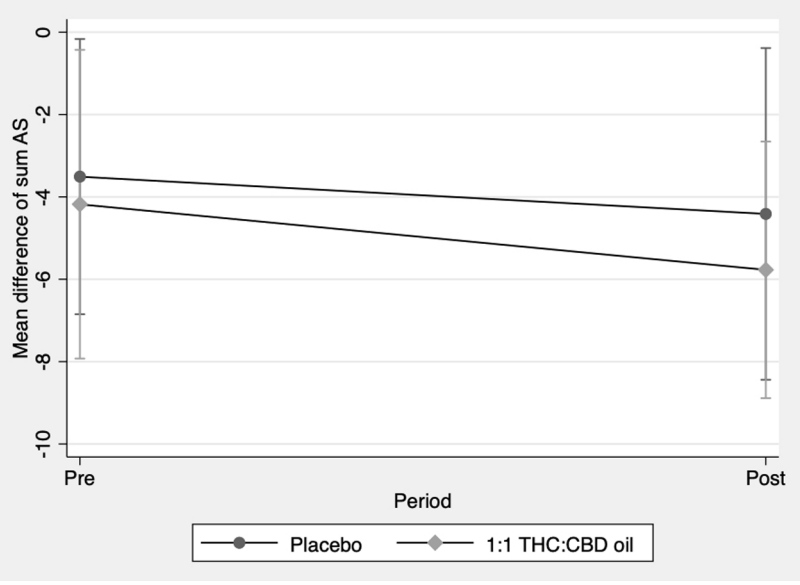

Figure 3. The effect of THC:CBD oil on the sum Ashworth Scale (AS).

the effect size of the THC:CBD oil on reducing spasticity was 1.7 (95%CI: −0.6 to 4.0) (small, non-significant effect size but in the opposite direction, that is, favoring the placebo). There was also no statistically significant difference in pre-to-post-treatment difference in SFS, Physician rating scale VAS, Patient rating VAS, and percentage of tibial H:M ratio of the right and the left side, between the intervention and the control phase (all $p > 0.05$; Wilcoxon signed-rank test, 95% CI of effect size including a null value of zero).

We conducted the adjusted analysis using a multi-level mixed-effect model with repeated measures, that is, controlling the period effect, sequence

Table 4. Comparisons of efficacy on reducing spasticity from the adjusted analysis.

Parameters	Effect size (95% confidence interval) from multilevel mixed-effect model (patient = random effect) controlled for period effect, sequence effect, and pre-treatment value	*p*-Value of intervention effect (one-tailed)
Summation of AS	−1.2 [−5.9 to 3.5]	0.309
SFSS	−0.02 [−0.4 to 0.4]	0.446
Physician rating VAS	−6.7 [−23.2 to 9.8]	0.073
Patient rating VAS	**−13.9 [−25.5 to −2.3]**	**0.010***
H:M ratio Rt (%)	8.0 [−14.3 to 30.3]	0.758
H:M ratio Lt (%)	−5.1 [−31.8 to 21.6]	0.355

Bolded and *Significant at $p < 0.05$ by multilevel mixed-effect model.
AS, Ashworth Scale; CBD, cannabidiol; H/M, H-response per M-response ratio; SFS, Spasm Frequency Scale; THC, tetrahydrocannabinol; VAS, visual analog scale.

effect, and pre-treatment value as a fixed effect and controlling the difference in each patient as a random effect (Table 4). For the primary outcome of sum AS, there was no statistically significant difference in sum AS between the intervention and the control phase in the multilevel mixed-effect model (mean effect size = −1.2 [95%CI: −5.9 to 3.5], $p = 0.309$). For the secondary outcomes, there was no statistically significant difference in SFS, Physician rating VAS, and percentage of tibial H:M ratio of the right and the left side, between the intervention and the control phase in the multilevel mixed-effect model (all $p > 0.05$). On the other hand, there was a statistically significant difference in patient rating VAS between the intervention and the control phase; that is, the intervention phase had a significantly lower patient rating VAS of spasticity than the control phase, with the mean effect size of −13.9 (95%CI: −25.5 to −2.3) from the multilevel mixed-effect model. These results indicate that the 1:1 THC:CBD oil can reduce the patient rating VAS of spasticity by 13.9 mm, or 18.5%, from the initial value of 75.0. Cohen's d of the patient rating VAS was −0.6, which indicated a medium effect size for spasticity reduction.

Discussion

Changes from the registered protocol

After screening 100 potential participants with only one recruited participant, we changed the study protocol aiming to improve the recruitment rate of the protocol. This included: (1) broadening the etiology of SCI (from a traumatic etiology only to either traumatic or degenerative spinal etiology as both of them share a stable clinical course after surgery); and (2) decreasing the severity of spasticity from AS > 2 to AS ⩾ 2. These changes may reduce internal validity of the study and may potentially induce the floor effect in those with less spasticity; however, we decided to trade off these problems for improving the recruitment rate.

Safety of the 1:1 THC:CBD oil

There was no statistically significant difference in safety outcomes between participants who received the THC:CBD intervention and those who received the placebo control. This safety result should be interpreted with caution due to an underpowered statistical analysis, as the sample size has been calculated according to the efficacy, not the safety outcome. This result was different from the previous studies reporting severe side effects resulting in study withdrawal.[3,17] In addition, a recent survey reported that cannabinoid use for spasticity introduced common adverse events including dry mouth, drowsiness, fatigue, dizziness, and nausea.[18] These may be due to differences in oil composition (THC:CBD vs THC alone), low dosage (maximal dose of 12 mg/day vs average dose of 31 mg/day), and the nature of the cannabinoids (natural extraction vs synthetic drug).[3,17,18]

Although there were no serious adverse events, an insignificant increase in non-serious adverse events, including hypotension, bradycardia, and elevated hepatic enzymes, makes the 1:1 THC:CBD oil at risk for use; an insignificant result can turn out to be significant if the sample size is increased. Despite excluding individuals with cardiovascular disease and/or hepatic disease, people with chronic SCI are still at risk of having cardiovascular and hepatic complications from medications,[19] and the risk should be increased if the individual has underlying cardiovascular and/or hepatic disease.

Efficacy of 1:1 THC:CBD oil on reducing spasticity

There was no statistically significant difference in the pre-to-post-treatment difference in summated AS from all muscles, which was the primary outcome, between the intervention and the control phase, together with no statistically significant difference in SFSS, Physician rating VAS, and tibial H/M ratio, indicating that there is no evidence demonstrating the efficacy of 1:1 THC:CBD oil on reducing spasticity in people with chronic SCI when evaluated using the physician-assessed. The 95% CI for all effect sizes included zero, indicating that the true effect may be null. These results are similar to those from the recent survey, which reported a null effect of cannabinoids on physical function in individuals with spasticity from various etiologies.[18] Although the study design of our study is different from the previous one, this consistent result addresses the questionable effect of cannabinoids on spasticity reduction.

These results differ from those of the previous clinical trial.[3,4,17] Some explanations for these inconsistent results should be discussed, including the differences in the study protocol, medication, and participants. First, all participants in this study were hospitalized and received physical and occupational therapy programs aiming to decrease spasticity; the control phase was not an inactive control, potentially leading to a ceiling effect of anti-spasticity treatment, causing an indifferent result in some participants. Notably, this protocol, despite having high internal validity because all potential confounding factors, such as additional treatments, were controlled, may differ from real-life OPD settings and may have low external validity or generalizability. Therefore, the effect of THC:CBD oil on spasticity reduction in people with chronic SCI in real-life OPD settings may be different from that in this study and should be further investigated.

For the differences in medication, the cannabinoids used in our study are 1:1 natural Thai extract THC:CBD, which is different from the previous studies showing an effective result. For example, one study used cannabis extract capsules containing 2.5 mg of THC and 1.25 mg of cannabidiol.[17] Another study used synthetic nabilone, a synthetic THC[4] and 9-THC (Dronabinol).[3] Noteworthy, all positive studies used THC as a single compound or THC with a ratio between THC and CBD more than that was used in this study (THC:CBD = 2:1 vs 1:1). Also, in contrast with the other study in people with SCI that used a synthesis of THC[3,4] and another study in MS,[17] our study used natural extract cannabinoids, which may deliver a lower potent medical dosage than a synthetic form or may not be stable enough to in maintain the efficacy due to oil formulation. Also, our cannabinoid dosage may not be adequate since we use 1:1 THC:CBD oil, 12 drops/day or 12 mg/day of THC and CBD as a maximum dosage due to unknown maximum and toxicity dosage in the oil in Thai people with SCI. For example, previous studies demonstrated that an average dosage for effectively reducing chronic pain was 19.2 mg for THC and 17.8 mg for CBD.[20,21] In addition, a previous study that used the same type of 1:1 THC:CBD oil demonstrated the effect of reducing spasticity in people with MS at the average dosage of 27.5 mg.[5] Therefore, an effect on spasticity reduction should be more expected in THC-predominated cannabinoids, and the dosage should be increased and may be up to 27.5 mg,[5] and increasing the maximum dosage should be considered in future efficacy studies.

Patient rating VAS was the only spasticity-related outcome responding to the THC:CBD intervention. Although it is not frequently used in spasticity research since it is subjective, patient rating VAS of the severity of spasticity was used in the previous study[4] and showed the same direction but a lower and non-significant effect size when compared with the sum AS assessment.[4] Despite being more subjective, the severity of spasticity evaluated by patient rating VAS may be directly related to the patient's life experience, even more than other objective, physician-evaluated outcomes. Since the patients evaluated the patient rating VAS of the

severity of spasticity by themselves, with a time frame from the instruction of "within 24 h," it may better reflect the 24-h spasticity experience of the patients, whereas all other assessments report spasticity cross-sectionally. These differences in domain and time frame of assessment may be responsible for the inconsistency between the patient rating VAS and other measures. Also, it should be hypothesized that more severe degree of spasticity when applying physical examination assessment may be resulted from increased sympathetic activity during facing healthcare providers similar to a condition of higher blood pressure levels when obtained by medical personnel compared to the levels obtained by themselves, or "White Coat Hypertension,"[22] as there is evidence demonstrating that increased sympathetic activities may induce more severe degree of spasticity in patients with upper motor neuron syndrome.[23]

Strengths and limitations

We accepted our limitations, including the difficulty measuring H-reflex, the potential underdosage of THC/CBD, and our inpatient study setting as previously described. To evaluate the risk of bias of this study, the Cochrane Risk of Bias (RoB) tool was applied.[24] As this study used a valid study design (crossover study for symptomatic treatment), randomization method (simple randomization), and allocation concealment (sealed envelope), there may not be problematic selection bias in this study. According to the performance bias, since the investigators, participants, outcome assessors, and analyzers were successfully blinded to the study group using a placebo with a similar appearance and odor, there should be no risk of performance bias. Regarding detection bias, since this study used both subjective and objective outcomes and employed effective allocation concealment and blinding, the risk of detection bias may be low. Since this study has no missing participants and the primary outcomes were reported according to the protocol, it may have a low risk of attrition and reporting bias. After considering all types of bias, this study has a low RoB.

Another limitation is that we cannot adjust for the effect of different rehabilitation programs and diverse concomitant antispastic medications. Physical exercise, occupational therapy, rehabilitation program, and concomitant medications are all confounding factors of the effect of cannabis.[25] However, our rehabilitation program, including physical exercise and occupational therapy, was personalized by different SCI characteristics and the present conditions of the participants. Therefore, it was different for each participant and for the same participant but on different days. We have tried to adjust the concomitant medications; however, because of the small sample size, only three participants had different medications from the others (receiving only baclofen). We then decided not to include concomitant medication status either as an adjustment factor or in a subgroup analysis to prevent invalid statistical inference due to violations of parametric statistical assumptions.[26] Further study with enough sample size is needed to demonstrate the effect of cannabinoids with adequate adjustment for these factors. The short administration period of 4 weeks may also be insufficient to produce long-term neurophysiological changes in individuals with chronic SCI, as the effects of cannabinoids on stimulating progenitor cells for remyelination and neuroregeneration, and inhibiting neuroinflammation, may require longer administration.[27]

To our knowledge, this is the first study evaluating the feasibility, safety, and efficacy of the naturally extracted Thai 1:1 THC:CBD oil in reducing spasticity in people with chronic SCI. The crossover study design equalized the baseline characteristics and the severity of spasticity of the participants then preventing a selection bias. The effectiveness of the washout period was checked by a urine cannabinoid test, which is very sensitive (50 ng/ml). Therefore, there was no risk of carry-over effect, which is the most important risk of a crossover study. Also, this study used standardized, multidimensional clinical and electrophysiological outcomes. This study also used cannabinoids as an add-on treatment, which correlates with the real-world setting where we do not stop standard treatments before starting alternative medication. The safety protocol in this study was thorough and can be applied in an IPD setting for safety concerns.

Clinical and research application

For clinical application, the benefits and the risks of using 1:1 THC:CBD oil should be individually justified before applying it in real-life clinical practice. For example, a 1:1 THC:CBD intervention should be considered in people with chronic SCI who have intractable spasticity that does not respond to any medical and surgical interventions

and also have no underlying cardiovascular disease and/or hepatic disease.

For research applications, as previously discussed, many gaps in knowledge are waiting for researchers to clarify. These issues include: (1) how to appropriately set inclusion and exclusion criteria, as well as stratification criteria, to accommodate the differences in mechanisms and characteristics of spasticity in people with SCI, as well as the severity of spasticity; (2) how to identify the proper dosage of THC and CBD, as well as its ratio, to maximize the spasticity reduction effect; and (3) how to select a spasticity-related outcome that is the most relevant to the patient's clinical situation and apply it as the primary outcome in future studies.

Conclusion

Results of this double-blind, placebo-controlled, crossover clinical trial demonstrate that, in people with chronic SCI who had intractable spasticity, there was no statistically significant effect of GPO 1:1 THC:CBD oil on spasticity-related outcomes, except a patient rating VAS reduction. Further studies aiming to prove the effect of 1:1 THC:CBD with a higher dosage of THC (more than 12 mg/day), as well as applying the patient rating VAS as the primary outcome, in people with chronic SCI who have intractable spasticity, should be conducted.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethics Committee of the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (Study ID: REH 2564 08541, obtained date 21 December 2021). All participants provided written informed consent to participate in this study.

Consent for publication

All participants provided written informed consent to publish results that include their deidentified data.

Author contributions

Nattha Boonthanakorn: Formal analysis; Investigation; Methodology; Project administration; Writing – original draft.

Sintip Pattanakuhar: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Pratchayapon Kammuang-lue: Investigation; Writing – review & editing.

Siam Tongprasert: Investigation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.*

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No generative AI was used during the development of this manuscript.

References

1. Adams MM and Hicks AL. Spasticity after spinal cord injury. *Spinal Cord* 2005; 43: 577–586.
2. Hsieh JTC, Connolly SJ, McIntyre A, et al. Spasticity following spinal cord injury. In Eng JJ, Teasell RW, Miller WC (eds) *Spinal cord injury rehabilitation evidence*. version 6.0. SCIRE – Spinal Cord Injury Research Evidence, 2016, pp. 1–135.
3. Hagenbach U, Luz S, Ghafoor N, et al. The treatment of spasticity with Delta9-tetrahydrocannabinol in persons with spinal cord injury. *Spinal Cord* 2007; 45: 551–562.
4. Pooyania S, Ethans K, Szturm T, et al. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. *Arch Phys Med Rehabil* 2010; 91: 703–707.
5. Aungsumart S, Pongsuthimanus N and Apiwattanakul M. A pilot study of the Government Pharmaceutical Organization (GPO) cannabis extract for multiple sclerosis (MS) spasticity treatment in Thailand. *J Med Assoc Thai* 2021; 104; 460–465.
6. Longoria V, Parcel H, Toma B, et al. Neurological benefits, clinical challenges, and neuropathologic promise of medical marijuana: a systematic review of cannabinoid effects in multiple sclerosis and experimental models of demyelination. *Biomedicines* 2022; 10: 539.
7. Uzair M, Qaiser H, Arshad M, et al. Neurobiology of cannabinoids and medical cannabis in therapeutic intervention for multiple sclerosis: understanding the molecular mechanisms of action. In: Zeine R and Teasdale B (eds) *Medical cannabis and the effects of cannabinoids on fighting cancer, multiple sclerosis, epilepsy, Parkinson's, and other neurodegenerative diseases*. Hershey (PA): IGI Global Scientific Publishing, 2023, pp. 187–216.
8. Stella N. THC and CBD: similarities and differences between siblings. *Neuron* 2023; 111: 302–327.
9. Lim CY and In J. Considerations for crossover design in clinical study. *Korean J Anesthesiol* 2021; 74: 293–299.
10. Orsnes G, Crone C, Krarup C, et al. The effect of baclofen on the transmission in spinal pathways in spastic multiple sclerosis patients. *Clin Neurophysiol* 2000; 111: 1372–1379.
11. Johnson GR. Outcome measures of spasticity. *Eur J Neurol* 2002; 9: 10–6, 53–61.
12. Baunsgaard CB, Nissen UV, Christensen KB, et al. Modified Ashworth scale and spasm frequency score in spinal cord injury: reliability and correlation. *Spinal Cord* 2016; 54: 702–708.
13. Matthews WB. Ratio of maximum H reflex to maximum M response as a measure of spasticity. *J Neurol Neurosurg Psychiatry* 1966; 29: 201–204.
14. Chow SC, Wang H and Shao J. *Sample size calculations in clinical research*. New York: Taylor & Francis 2003, pp. 63–68.
15. Álvarez-Marcos F, Santos L and Clerc O. Chapter 11: Meta-analysis. In Fregni F, Sanchez A, Fandino W and Loss K (eds) *262 Questions for deeper statistical learning through questioning*, 2022.
16. Dwan K, Li T, Altman DG, et al. CONSORT 2010 statement: extension to randomised crossover trials. *BMJ* 2019; 366: l4378.
17. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry* 2005; 76: 1664–1669.
18. Nastatos XL, Schubert EA and Wheate NJ. Investigating the effectiveness and adverse events of medicinal cannabis for patients with muscle spasticity or spasms. *J Pharmacol Exp Ther*. 2026; 393: 103780.
19. Myers J, Lee M and Kiratli J. Cardiovascular disease in spinal cord injury: an overview of

prevalence, risk, evaluation, and management. *Am J Phys Med Rehabil* 2007; 86: 142–152.

20. Ueberall MA, Essner U and Mueller-Schwefe GH. Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German Pain e-Registry. *J Pain Res* 2019; 12: 1577–604.
21. Petzke F, Tölle T, Fitzcharles MA, et al Cannabis-based medicines and medical cannabis for chronic neuropathic pain. *CNS Drugs* 2022; 36: 31–44.
22. Pioli MR, Ritter AM, de Faria AP, et al. White coat syndrome and its variations: differences and clinical impact. *Integr Blood Press Control* 2018; 11: 73–79.
23. Hung CY, Tseng SH, Chen SC, et al. Cardiac autonomic status is associated with spasticity in post-stroke patients. *NeuroRehabilitation* 2014; 34: 227–233.
24. Nejadghaderi SA, Balibegloo M and Rezaei N. The Cochrane risk of bias assessment tool 2 (RoB 2) versus the original RoB: a perspective on the pros and cons. *Health Sci Rep* 2024; 7: e2165.
25. Hoch E, Volkow ND, Friemel CM, et al. Cannabis, cannabinoids and health: a review of evidence on risks and medical benefits. *Eur Arch Psychiatry Clin Neurosci* 2025; 275: 281–292.
26. Hopkins S, Dettori JR and Chapman JR. Parametric and nonparametric tests in spine research: why do they matter? *Global Spine J* 2018; 8: 652–654.
27. Valeri A and Mazzon E. Cannabinoids and neurogenesis: The promised solution for neurodegeneration? *Molecules* 2021; 26: 6313: 1–26.