Original Article

A Pilot Study of the Government Pharmaceutical Organization (GPO) Cannabis Extract for Multiple Sclerosis (MS) Spasticity Treatment in Thailand

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Background: The prevalence of spasticity in multiple sclerosis (MS) patients is nearly 90%. Most patients do not respond to current anti-spastic medications.

Objective: To evaluate the efficacy and safety of Government Pharmaceutical Organization cannabis extract (GPOCE) in the treatment of spasticity in MS patients in Thailand.

Materials and Methods: This prospective pilot study in patients diagnosed with MS whose spasticity was not relieved under current spasticity treatments, was performed between November 2019 and June 2020. The GPOCE formulation of THC:CBD 1:1 was administered to all patients. The treatment outcomes were determined at 12 weeks and compared with their baseline.

Results: Seven patients participated in the present study. Among these, two patients withdrew after receiving only a small dose of GPOCE. Finally, five patients were included in the final analysis. The primary outcome was a reduction in the Modified Ashworth Score (MAS), which decreased among participants from a baseline of 15 (IQR 12 to 19) to 6 (IQR 1 to 12) (p=0.043). The key secondary outcome was a clinically relevant response (CRR), which was defined as a reduction of the spasticity Numeric Rating Scale (NRS) of more than thirty percent compared to baseline. Four patients (80%) achieved CRR. Moreover, the overall spasticity NRS decreased from a median of 6 (IQR5 to 7) to 2 (IQR2 to 3). A reduction of other NRS parameters, including fatigue, pain, tremor, sleep, spasm, anxiety, and depression, was also observed after treatment. Moreover, GPOCE was generally well tolerated.

Conclusion: GPOCE is useful in treating spasticity in patients with MS. The safety profile is acceptable under the supervision of a health care provider.

Keywords: Multiple sclerosis (MS), Cannabis extract, Spasticity

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Multiple sclerosis (MS) is a chronic inflammatory immune-mediated disease that affects the central nervous system. In Thailand, the prevalence of MS is approximately 0.2 per 100,000[(1)], resulting in a financial burden for both patients and the government. One of the most common symptoms affecting patients' quality of life is spasticity, which has a prevalence of nearly 90%[(2)]. This symptom often leads to pain, distress, and worsening body movement, impairs activities of daily living, and decreases quality of life.

There are many types of antispasmodics used to treat MS, such as baclofen, tizanidine, dantrolene, benzodiazepine, and anticonvulsants. Nevertheless, most patients do not respond and stop using because of side effects, leading many patients to seek out alternative treatment options such as cannabis extracts. There is evidence from various phase III clinical studies[(3-8)] and subsequent support from a meta-analysis[(9)] demonstrating that cannabis extracts play an essential role in spasticity relief in MS.

The cannabis extract approved to treat spasticity, nabiximols, was developed by GW Pharmaceuticals. The cost of treatment is relatively high at approximately 20,000 to 30,000 Thai Baht (THB), depending on dosage and frequency. Moreover, there is no data regarding the use of cannabis extracts in patients with MS in Thailand. Government Pharmaceutical Organization cannabis extract (GPOCE) contains the same formula as nabiximols (THC:CBD 1:1) and is available in Thailand at a lower price. Thus,

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the present study aimed to evaluate the efficacy and safety of GPOCE in the treatment of spasticity in MS patients in Thailand.

Materials and Methods

Patients

The present study was an observational prospective pilot study conducted between November 1, 2019 and June 30, 2020 at the Prasat Neurological Institute, a tertiary neurologic referral center in Bangkok, Thailand. The patients, who met the diagnostic criteria for MS according to the 2017 McDonald's diagnostic criteria, had follow-up visits for at least three months. Other inclusion criteria were age between 25 and 60 years, stable disease for at least six months, Modified Ashworth Score (MAS) of at least 2 in lower limb muscles, and non-responder to antispasmodic medication. The exclusion criteria were patients who had a history of drug abuse, previous cannabis use, impaired cognitive function, and underlying heart disease such as coronary artery disease and arrhythmias. The Ethics Committee at Prasat Neurological Institute approved the present study, the approval number 63029. Written informed consent was obtained from all the enrolled patients.

Study conduct

Before treatment, all patients underwent a baseline evaluation consisting of MAS, Numerical Rating Scale (NRS) for spasticity, fatigue, pain, tremor, insomnia, tonic spasm, anxiety, depression, and EQ-5D5L. The initial assessment also included a 12-lead EKG, complete blood count, liver function tests, creatinine, and blood urea nitrogen.

All the patients received the GPOCE formulation THC:CBD 1:1 (2.7 mg: 2.5 mg: 0.1 mL). Other GPOCE elements, such as terpenes and flavonoids, were not listed by the manufacture. The starting dose was 0.1 mL in the first week. During the second week, the dosage increased to 0.1 mL twice a day for three days. After the second week, the dosage could be increased every three days but not more than 1.5 times the previous dosage, with the time between doses of not less than four hours. The maximum allowable dosage was 1 mL per day, equivalent to 27 mg THC and 25 mg of CBD. In the case of a patient not being able to tolerate a side effect, the daily dose was reduced to the previous dosage until the side effect resolved. After resolution, patients could either resume dose escalation or remain at the dosage they were at prior to the onset of side effects. However, if the patient increased the dose again and the side effects returned, the dose was reduced with no further increase in dose allowed. Assessment of side effects and laboratory tests were completed at the end of weeks 1, 3, and 8, and outcomes were assessed at the end of week 12.

The primary outcome was the change in spasticity at week 12 using the MAS. The MAS is the most universally accepted clinical tool used to measure the increase in muscle tone. The score is assessed to be 0 to 5 with 0: normal tone, 1: minimal resistance throughout less than half of ROM, 2: more marked increase in muscle tone through most of the ROM, 3: passive movement difficult, and 4: rigid in flexion or extension. Ten muscle groups on each side are assessed, which are elbow flexion, elbow extension, pronation, supination, wrist flexion, finger flexion, hip adduction, knee flexion, knee extension, and foot plantar flexion. The reliability of MAS depends on the assessor's experience, so the authors used the same assessors for each patient.

The secondary outcome was assessed using NRS 0 to 10 for spasticity, fatigue, pain, tremor, insomnia, tonic spasm, anxiety, and depression, with 0 meaning no symptoms and 10 meaning most severe symptoms. However, the current standard assessment of cannabis in MS has shifted toward the NRS spasticity score, which has been validated for use in MS clinical trials[10]. This use is generally accepted and was used as the primary endpoint in the trial of nabiximol effectiveness[3-7]. The clinically relevant response (CRR) threshold was defined as 30% of more NRS spasticity score improvement over baseline value. The authors selected the CRR as a key secondary outcome in the present study. The EQ-5D5L was used to assess quality of life. Finally, the Global Impression of Change (GIC) scale for spasticity and pain was used to determine impression of change after treatment.

Statistical analysis

Frequency data were reported as a number with percentage, and continuous data were expressed as a median and interquartile range (IQR). Change from baseline for primary and secondary outcomes was analyzed using related sample Wilcoxon signed-rank test. Statistical analysis was performed in SPSS Statistics, version 17.0 (SPSS Inc., Chicago, IL, USA). The significance level was set at p-value less than 0.05.

Results

Demographic data

Seven patients with MS diagnosed according to

Table 1. Baseline clinical characteristic

Patients	Sex	Age (years)	Phenotype	Age of onset (years)	Duration (years)
1	Male	42	PPMS	40	2
2	Female	49	SPMS	47	2
3	Male	39	SPMS	37	2
4	Male	42	SPMS	18	25
5	Female	40	SPMS	33	7
6	Female	44	RRMS	30	14
7	Female	60	SPMS	45	15

PPMS=primary progressive multiple sclerosis; SPMS=secondary progressive multiple sclerosis; RRMS=relapsing-remitting multiple sclerosis

Table 2. Total MAS (primary outcome), lower extremities MAS, and spasticity NRS compared between baseline and 12 weeks after treatment for each patient. Percent spasticity NRS change >30% was considered to be a clinically relevant response (key secondary outcome)

Patients	Total MAS			Lower extremities MAS			Spastic NRS		
	Baseline	Week 12	Change	Baseline	Week 12	Change	Baseline	Week 12	Percent change
1	12	1	11	12	1	11	10	2	80
2	24	16	8	22	14	8	5	2	60
3	19	12	7	18	12	6	7	3	57
6	15	6	9	9	2	7	4	3	25
7	6	1	6	6	1	5	6	0	100
Median (IQR)	15 (12 to 19)	6 (1 to 12)	8 (7 to 9)	12 (9 to 18)	2 (1 to 12)	7 (6 to 8)	12 (9 to 18)	2 (1 to 12)	60 (57 to 80)

MAS=modified Ashworth score; NRS=numeric rating scale; IQR=interquartile range

the 2017 McDonald's criteria and followed at Prasat Neurological Institute participated in the present study. The demographic data are summarized in Table 1. The participants included four females (57.1%) and three males (42.8%) with a median age 42 years (IQR 40 to 42). Five patients were diagnosed with secondary progressive MS, one with primary progressive MS, and one with relapsing-remitting MS. Disease duration ranged from 2 to 25 years.

Primary outcome

Two of the seven enrolled patients withdrew from the study after receiving only a small dose of GPOCE (0.5 mL: 1.35 mg THC and 1.25 mg CBD). Patient no.4 withdrew due to difficulty walking, and patient no.5 withdrew due to increasing central neurogenic pain. Ultimately, only five patients from the study were included in the final analysis. However, there was a dramatic decrease in MAS in all five of those patients (Table 2). The median total MAS score decreased from a baseline of 15 (IQR 12 to 19) to 6 (IQR 1 to 12) over the 12 weeks of treatment (Figure 1A). The decrease in MAS was prominent in the lower extremities, with a reduction from a median 12 (IQR 9 to 18) to 2 (IQR 1 to 12) after treatment (Figure 1B). Even though the study included only a small number of patients, there was a statistically significant reduction of total MAS and lower extremities MAS.

Secondary outcome

The patient reported NRS, GIC, and quality of life were used to assess the secondary outcomes of GPOCE treatment (Table 3). As patient-reported NRS is a current standard assessment tool for cannabis treatment, NRS was a key secondary outcome in the present study. A reduction in spasticity NRS of more than thirty percent compared to baseline was considered to be a CRR[10]. Four of the five patients, or 80%, had a CRR (Table 2), which is correlated with the primary outcome. Moreover, the overall NRS for spasticity significantly decreased from a median 6 (IQR 5 to 7) to 2 (IQR 2 to 3) over the 12 weeks of treatment (p=0.043). A reduction of other NRS parameters, including fatigue, pain, tremor, sleep, spasm, anxiety, and depression, were also observed after treatment, although these results did not achieve statistical significance. Meanwhile, GIC for both pain

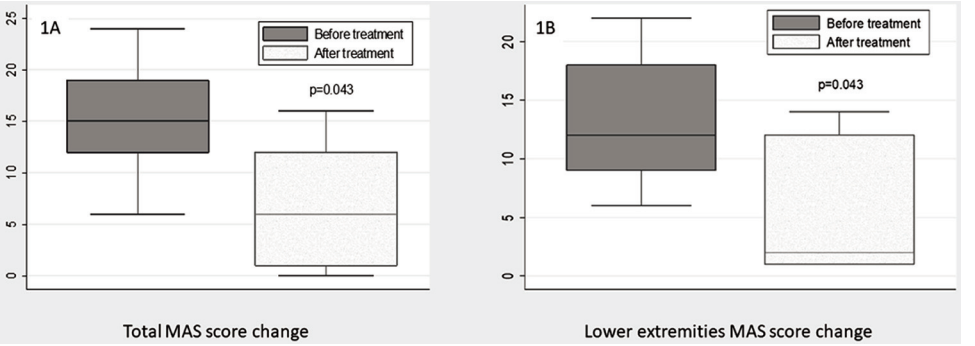

Figure 1. The total MAS (1A) and lower extremities MAS (1B) score change after 12 weeks of treatment. MAS=modified Ashworth score

Table 3. Other secondary outcomes include NRS 0 to 10 for spasticity, fatigue, pain, tremor, insomnia, tonic spasm, anxiety, and depression. Clinical utility was assessed using EQ-5D5L and GIC scale for spasticity and pain

	Before treatment; median (IQR)	After treatment; median (IQR)	p-value
NRS			
1. Spasticity	6 (5 to 7)	2 (2 to 3)	0.043[a]
2. Fatigue	4 (3 to 5)	0 (0 to 2)	0.066
3. Pain	4 (2 to 5)	0 (0 to 2)	0.18
4. Tremor	5 (0 to 5)	0 (0 to 1)	0.109
5. Sleep	7 (0 to 8)	0 (0 to 0)	0.109
6. Spasm	2 (0 to 5)	0 (0 to 0)	0.18
7. Anxiety	2 (0 to 3)	0 (0 to 0)	0.109
8. Depression	1 (0 to 3)	0 (0 to 0)	0.109
GIC spasticity		5 (4 to 7)	
GIC pain		6 (4 to 6)	
Utility	0.70 (0.64 to 0.81)	0.81 (0.77 to 0.82)	0.144

IQR=interquartile range; NRS=numeric rating scale; GIC=global impression of change

[a] Level of significance p<0.05

and spasticity were high, with medians of 6 (IQR 4 to 6) and 5 (IQR 4 to 7), respectively. These data indicated that the patients experienced a moderately large treatment effect. However, overall quality of life, as determined by EQ-5D5L was not affected by the GPOCE treatment.

Safety and tolerability

There was one serious adverse event, which was definitively diagnosed as hyperemesis syndrome. The patient developed symptoms of severe nausea and vomiting at 24 weeks after treatment initiation. She was admitted for supportive care for five days and discontinued GPOCE. There were other minor adverse events, including hypersomnolence (80%), dry mouth (60%), dizziness (40%) palpitation (20%), loss of appetite (20%), and euphoria (20%).

Discussion

In the present open-label pilot study, the authors found that the GPOCE formulation THC:CBD 1:1 improved spasticity in patients with MS. There was an objective reduction in MAS on assessment by physician. The reduction in MAS was observed in all five patients who remained in the study, which were considered to have had a clinical response in the primary outcome. The median change in MAS score e after treatment was large at 8 (IQR 7 to 9). However, the standard assessment of cannabis use in MS treatment has shifted toward the NRS spasticity score, which has been validated for use in MS clinical trials[10]. The NRS for spasticity is generally accepted and was used as the primary endpoint in the trial of nabiximol effectiveness[3-7]. CRR was defined as 30% or more NRS spasticity score improvement over the baseline value. Eighty percent of the patients in the present study achieved a CRR. Even though, there were only a small number of patients in the present study, this initial investigation indicated the efficacy of the GPOCE formulation of THC:CBD 1:1 in improving spasticity in patients with MS. Moreover, the previous trial of nabiximol reported an approximately 35% to 40%[3-8] improvement, but the present study demonstrated a high response rate at 80%. This difference may be explained by the bias of an open-label study compared to the previous randomized control trial.

In the present study, the authors decided to use MAS instead of the NRS spasticity score as the primary outcome, even though the previously published study considered that MAS is not a good

indicator for determining the clinical response to cannabis in patients with MS. The Ashworth score has several limitations, and it is not possible to capture the highly complex aspects of spasticity with it[8]. However, the present study found a statistically significant improvement in Modified Ashworth, which might be possible to explain as 1) the patients in the present study had high baseline spasticity. Therefore, the change in MAS score after treatment may be more detectable compared to the previous study, 2) because of the small sample size, the present study had only one clinician assessing the MAS compared with other studies which had more than one assessor. Thus, the present study did not have interrater bias from different assessors, 3) some previous studies used different components, dosage, route of administration, or type of cannabis extraction, which might lead to a different outcome with regards to spasticity[9,11].

Moreover, the decision to use MAS as the primary outcome in the present study was because GPOCE was a different medication produced by a pharmaceutical company in Thailand. This is distinct from nabiximol, which is the standard cannabis extract used to treat spasticity in MS in terms of production and route of administration. Moreover, the treatment of various diseases with cannabis is currently constrained by politics. Using an assessment method with an objective evaluation, such as MAS, was more suitable under these circumstances. The standard subjective NRS spasticity score was also used in parallel to determine the efficacy of cannabis in the present study.

In addition, there was improvement in other secondary outcomes, including fatigue, pain, tremor, sleep, spasm, anxiety, and depression, which correlated with patients' impression of change as indicate by GIC in both pain and spasticity. However, the overall quality of life, as assessed by EQ-5D, was not affected even though the clinical parameters were shown to have significantly improved. Two main points of view can explain this result. The first one is a small sample size of patients not providing enough statistical power in the present study. The second view is GPOCE provides relief spasticity and pain but not the other element of the generic EQ5D5L, especially mobility, self-care, or daily activities. To solve this problem, a disease-specific questionnaire such as MS Quality of Life-54 (MSQOL-54) might be better than EQ5D5L to detect the quality of life improvement in further study. However, in the previously published study, a randomized control trial showed clinical benefit from cannabis without improvement in the quality of life, as assessed by EQ-5D[3,4].

Not surprisingly, the adverse event rate from cannabis extract use was high at 80%. This result was similar to the previous study, in which the rate of any adverse event was as high as 93%[3,7] in the cannabis treatment group. However, these side effects are usually mild, with the most reported problems being dry mouth, hypersomnolence, and dizziness. In addition, the discontinuation rate in the present study was 20% due to hyperemesis syndrome. Other discontinuation rates in cannabis extraction studies due to an adverse event have varied from 3% to 21%[3-5,7].

The present study is the first to report on the efficacy of GPOCE in the treatment of spasticity in patients with MS. However, only a small sample size was enrolled. GPOCE leads to benefits in both objective and subjective aspects in the treatment of spasticity in Thai patients with MS. These findings on both the efficacy and side effects of GPOCE suggest that GPOCE is likely to have similar characteristics to nabiximol, which is the drug approved to treat spasticity in MS produced by GW Pharmaceuticals. However, the price of GPOCE is cheaper than nabiximol at around one-tenth the cost. Thus, the cannabis extract produced by the Thai Pharmaceutical Company might play an essential role in treating spasticity in patients with MS not only in Thailand but also in low- and middle-income countries.

There were several limitations to the present study due to being only study in a small number of patients and had no control group. The treating physician and the physician providing outcome assessment were the same person, causing response bias, which can explain why the efficacy of the medication was higher than the previous study at 80% versus 35% to 40%. Moreover, the present study enrolled patients during the COVID-19 pandemic, so only a small number of patients volunteered for the present clinical study. Further studies on GPOCE, utilizing a randomized, double-blind controlled trial design, should be performed to prove the efficacy and safety of this medication.

In conclusion, GPOCE is effective in treating spasticity in patients with MS. The safety profile is acceptable under the supervision of a health care provider. The price of this product is lower than the currently approved cannabis extract nabiximol from GW Pharmaceuticals, and might provide benefits for patients with MS in Thailand and other low- to middle-income countries.

What is already known on this topic?

Spasticity is one of the most common symptoms that affect MS patients' quality of life. Most patients do not respond to the current antispasmodic drugs. Cannabis has been proven to relieve spasticity in MS in various clinical studies, supported by a meta-analysis. However, the price of the previously approved cannabis extraction for the treatment of spasticity, namely, nabiximols, is relatively high at approximately 20,000 to 30,000 THB per month.

What this study adds?

This study investigated the efficacy and safety of GPOCE in the treatment of spasticity in MS patients in Thailand. GPO cannabis extract is effective in treat spasticity in patients with MS. The safety profile is acceptable under the supervision of a health care provider. The price of this product is lower than the currently approved cannabis extract nabiximol from GW Pharmaceuticals and might provide benefits for patients with MS in Thailand and other low- to middle-income countries.

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Conflicts of interest

The authors declare no financial or other conflicts of interest.

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