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

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Abstract

Background: The prevalence of spasticity in multiple sclerosis patients is nearly 90%. Most of the patients didn't respond to the current anti-spastic drug.

Objective: The objective of this study is to evaluate the efficacy and safety of Government Pharmaceutical Organization cannabis extraction (GPOCE) in the treatment spasticity of MS patients in Thailand.

Materials and Methods: The prospective pilot study in the patient diagnosis with MS, who not relieved spasticity under current anti-spastic treatment, was performed between November 2019 and June 2020. The GPOCE formulation of THC: CBD1:1 was administration in all patients. The treatment outcomes were determined at 12 weeks to compare with their baseline.

Results: Seven patients participated in the study. Among these, two patients were withdrawn from this study after receiving only a small dose of GPOCE. Finally, five patients were included in the final analysis. The primary outcome was the reduction in modified Ashworth score (MAS) was decreased from baseline 15 (IQR 12-19) to 6 (IQR 1-12) (p=0.043). The key secondary outcome was a clinically relevant response (CRR), which define by reduction of spastic numeric rating scale (NRS) of spasticity more than thirty percent compared to baseline. Four patients (80%) achieved CRR. Moreover, the overall NRS of spasticity decreases forms the median 6 (IQR5-7) to 2 (IQR2-3). The reduction of other NRS parameters, including fatigue, pain, tremor, sleep, spasm, anxiety, and depression, were also observed after treatment. Moreover, GPOCE was generally well tolerated.

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

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Introduction

MS (MS) is a chronic inflammatory immune-mediated disease that affected the central nervous system. In Thailand, the prevalence of MS is about 0.2 per 100,000[1], resulting in the financial burden of patients and the government. One of the most common symptoms that affect patients' quality of life is spasticity which prevalence is nearly 90%.[2] These symptoms often lead to pain, distress, and worsening body movement, impair activities of daily living, and decrease quality of life.

There are many types of anti-spastic medication in MS, such as Baclofen, Tizanidine, Dantrolene, Benzodiazepine, and anticonvulsants. Nevertheless, most of the patients usually not respond and withdraw because of their side effects, so many patients try to find alternative treatments option, which is cannabis extraction. There are evidence form various phase III clinical studies[3-8], and subsequent support by the meta-analysis[9] demonstrates that cannabis extraction paly an essential role in relief spasticity in MS.

However, the price of approved cannabis extraction to treatment spasticity was developed by GW pharmaceutical company, namely Nabiximols. The cost of treatment is relatively high; approximately 20,000-30,000 Thai baht (THB) depend on dosage and frequency use. Moreover, there is no data regarding the cannabis extraction of patients with MS in Thailand. Because Government Pharmaceutical Organization cannabis extraction (GPOCE) contains the same formula as Nabiximols (THC: CBD 1:1), it was available in Thailand at a lower price. Thus, our study aims to evaluate the efficacy and safety of GPOCE in the treatment of spasticity of MS patients in Thailand.

Materials and Methods

Patients

This study is prospective pilot observational study conduct between 1st November 2019 and 30th June 2020 in the Prasat Neurological Institute, a tertiary referral neurological center in Bangkok, Thailand. The patients who fulfilled the diagnostic criteria of MS according to the McDonald's diagnostic criteria 2017, had follow-up visits for at least three months. Other inclusion criteria are age between 25-60 years, stable disease for at least six months, Modified Ashworth score at least 2 in lower limb muscles, and non-respond to the anti-spastic medication. The exclusion criteria were patients who had a history of drug abused, previous report use of cannabis, impair cognitive function, and underlying heart disease (coronary artery disease, arrhythmias). The Ethics committee approved this study at Prasat Neurological Institute with approval number 63029. Written informed consent was obtained from all the enrolled patients.

Study conduct

Before treatment, all patients undergo baseline evaluation consisted of Modified Ashworth score (MAS), Numerical Rating Scale (NRS) for spasticity, fatigue, pain, tremor, insomnia, tonic spasm, anxiety, depression, and EQ-5D5L. The initial assessment also includes EKG 12 leads, complete blood count, liver function test, creatinine, and blood urea nitrogen.

All of the patients receive GPOCE formulation THC: CBD 1: 1 (2.7mg: 2.5 mg: 0.1ml). The starting dose was 0.1 ml in the first week. The subsequent dose started in the second week by increase the dosage to 0.1 ml twice a day for three days. Then the dosage can be increased every three days but

does not exceed 1.5 times the previous dosage, and the time between dosage not lower than 4 hours. The maximal allowable dosage was 1 ml per day, equivalent to 27 mg THC and 25 mg of CBD. In the case of the patient cannot an intolerable side effect, the daily dose was reduced to the previous dosage until the side effect resolved. After resolution, patients have a right to further dose escalation or stop at the previous dosage before side effects occur. However, if patient escalation and side effects returned, the dose was reduced with no further increase dose allow. Side effects and laboratory assessment was done at the end of week 1,3 and 8, and the outcome assessment was undertaken 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 of muscle tone. The score consists of 0-5 (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, 4: rigid in flexion or extension). Ten muscle groups on each side were assessed (elbow flexion, elbow extension, pronation, supination, wrist flexion, finger flexion, hip adduct, knee flexor, knee extensor, foot plantar flexor). The reliability of MAS depends on the assessor experience, so we use the same assessors for each patient.

The secondary outcome includes NRS 0-10 in the item of spasticity, fatigue, pain, tremor, insomnia, tonic spasm, anxiety, and depression, which 0 means no symptoms and 10 mean most severity. However, the current standard assessment of cannabis in MS was shifted toward the NRS spasticity score, which has been validated to use in MS clinical trials.[10] There are generally accept and use as the primary endpoint in the trial of Nabiximol effectiveness.[3-7] The term clinically relevant response (CRR) threshold was defined as ≥30% NRS spasticity score improvement versus baseline value. We selected the CRR as a key secondary outcome in our study. The EQ-5D5L were used to assess the quality of life. Finally, the Global impression of change (GIC) scale for spasticity and pain use to determine to stratify of change after treatment.

Statistical analysis

The frequency data are reported as the number with percentage, and the continuous data are expressed as the median and interquartile range (IQR). Primary and secondary outcomes were compared from baseline to endpoints conducted using related sample Wilcoxson signed-rank test. Statistical analysis was analyze using the SPSS software (Version 17.0). The level of significance was set at P-value < 0.05.

Results

Demographic data

Seven MS patients defined by McDonald's criteria diagnosis 2017, followed up at Prasat Neurological Institute were participated in this study. The demographic data were summarized in Table 1. They were four females (57.1%) and three males (42.8%), median age 42 years (IQR 40-42). Five patients define as secondary progressive MS, one with primary progressive MS and one relapsing-remitting MS patients. The disease duration was the range from 2-25 years.

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 MS, SPMS: Secondary progressive MS, RRMS: Relapsing-remitting MS

Primary outcome

Of all seven patients, two patients were withdrawn from this study after receiving only a small dose of GPOCE (0.5 ml: 1.35 mg THC and 1.25 mg CBD). There were patient no.4 because of difficulty in walking and patient no.5 due to increasing central neurogenic pain. Finally, only five patients were included in the study for the final analysis. However, there is a dramatic decrease in MAS in all five patients (Table 2). The median total MAS score was decreased from baseline 15 (IQR 12-19) to 6 (IQR 1-12) in 12 weeks after treatment (Figure 1A). The decrease of MAS was prominent in the lower extremities with a reduction from median 12(IQR 9-18) to 2(IQR 1-12) after treatment (Figure 1B). Even though a small number of patients, there was statistical significance in the reduction of total MAS and lower extremities MAS.

Secondary outcome

The patient report NRS, GIC, and quality of life were used to determine the secondary outcome of GPOCE (table3). Consider patients reported NRS as a current standard assessment of cannabis treatment, which defines a key secondary outcome in this study. The reduction of spastic NRS more than thirty percent compared to baseline was considered as the clinically relevant response (CRR).[10] Four from five patients or 80 percent were recognized as CRR (Table 2), which correlates to the primary outcome. Moreover, the overall NRS of spasticity significantly decreases form the median 6 (IQR5-7) to 2 (IQR2-3) in 12 weeks after treatment (p=0.043). The reduction of other NRS parameters, including fatigue, pain, tremor, sleep, spasm, anxiety, and depression, also observed after treatment even though there was no statistical significance. Meanwhile, GIC in both pain and spasticity were high as median 6 (IQR 4-6) and 5 (IQR4-7), respectively. This data indicates the patient moderately high stratification of treatment effect. However, the overall quality of life which determine by EQ-5D5L was not affected by the GPOCE.

Safety and tolerability

There was one serious adverse event in which a definite diagnosis was hyperemesis syndrome. The patient developed symptoms of severe nausea vomiting after 24 weeks after treatment. She had to admit supportive care five days and discontinued GPOCE. The others were minor adverse events, including hypersomnolence (80%), dry mouth (60%), dizziness (40%) palpitation (20%), loss of appetite (20%), and euphoria (20%).

Table 2 Total MAS (primary outcome), lower extremities MAS, and spastic NRS compare between baseline and 12 weeks after treatment form each patient. Percent spastic NRS change > 30% considered as the 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 (12-19)	6 (1-12)	8 (7-9)	12 (9-18)	2 (1-12)	7 (6-8)	12 (9-18)	2 (1-12)	60 (57-80)

MAS: Modified Ashworth score, NRS: numeric rating scale, IQR: Interquartile range

Table 3 Other secondary outcomes include NRS 0-10 in the item of spasticity, fatigue, pain, tremor, insomnia, tonic spasm, anxiety, and depression. The utility obtains form EQ-5D5L and GIC scale for spasticity and pain.

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

IQR: Interquartile range, NRS: numeric rating scale, GIC: the global impression of change

[a] level of significance $p<0.05$

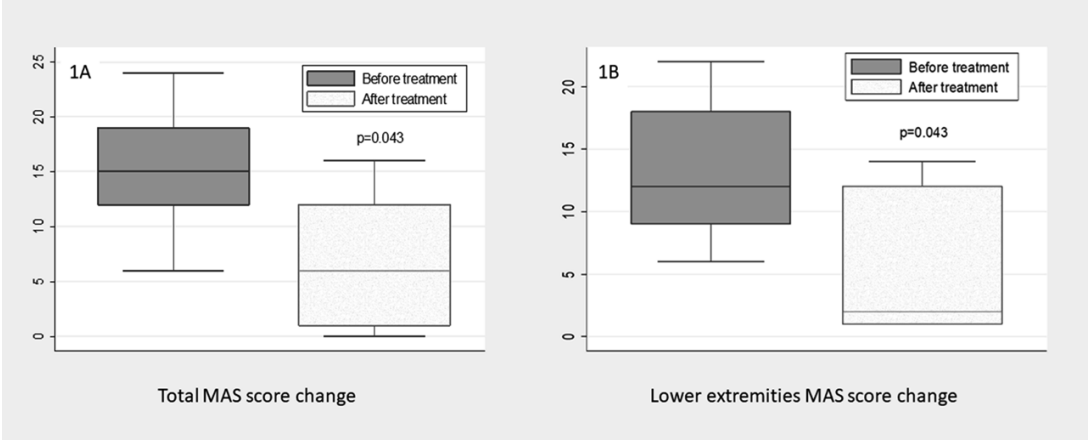

Figure 1 The total MAS (1A) and lower extremities MAS (1B) score change in 12 weeks after treatment. MAS: Modified Ashworth

Discussion

In this open-label pilot study, we found the significant effect of GPOCE formulae THC: CBD ratio 1:1 oil improve spasticity in patients with MS. There was a reduction in the objective view of physician assessment or MAS. The reduction of MAS was observed in all five patients who remain in the study. In other words, all patients were considered as the clinical response in the primary outcome. The median score change after treatment was high as eight and IQR 7-9. However, the current standard assessment of cannabis in MS was shifted toward the NRS spasticity score, which has been validated to use in MS clinical trials.[10] There are generally accept and use as the primary endpoint in the trial of Nabiximol effectiveness.[3-7] The term clinically relevant response (CRR) threshold was defined as ≥30% NRS spasticity score improvement versus baseline value. Eighty percent of the patients in our study were compatible with CRR. Even though we have a small number of patients, but this initial investigation indicates the efficacy of GPOCE formulae THC: CBD ratio 1:1 effective in improving spasticity in patients with MS. Moreover, the efficacy of Nabiximol previously reported approximately 35-40%[3-8] improvement, but our study demonstrates a high response rate as high as 80 %. This data might be possible to explain by the bias of open-label study compare to the previous randomized control trial group.

In this study, we decide to use MAS instead of the NRS spasticity score as the primary outcome, even though the previously published study considers MAS is not a good indicator to determine the clinical response of cannabis in patients with MS. The Ashworth score has several limitations and not possible to capture the highly complex symptoms of spasticity.[8] However, our study found a statistically significant improvement of Modified Ashworth might explain in the context of 1) The patient in our study has high baseline spasticity. Therefore the change in MAS score after treatment may be detectable compared to the previous study. 2) Because of the small sample size, our study has only one clinician to assess the MAS score compared with other studies that have more than one assessor. Thus our study did not have the inter-rater bias from different assessors. 3) Some data demonstrate different components, dosage, route of administration, or type of cannabis extraction that might affect a different outcome of spasticity.[9, 11]

Moreover, the decision to use MAS as the primary outcome in our study was based on the reason GPOCE was a different medication that produces under the pharmaceutical company in Thailand. There was different form the Nabiximol, which was the standard cannabis extraction to treat spasticity in MS in terms of production and route of administration. Moreover, the current situation of cannabis in terms of various treatment disease was constrained by politics. To use the tool contain objective evaluation like MAS was more suitable under these circumstances. In parallel, the standard subjective NRS spasticity score was also used to determine the efficacy of cannabis in this study.

Besides, there was improve other secondary outcomes, including fatigue, pain, tremor, sleep, spasm, anxiety, and depression correlate with patients' impression of change indicate by GIC in both pain and spasticity. However, the overall quality of life assess by EQ-5D was not affected even though the clinical parameter is shown significantly improve. This data reflects two main points

of view. The first one is a clinical improvement by cannabis didn't affect the overall quality of life. Suggest cannabis improve spastic and pain but not in the mobility, self-care, or usual activity. The second was patients prefer to respond to the outcome than the actual effect of medication positively because of open-label bias. However, the previously published article, even the randomized control study showed clinical benefit from cannabis but not the quality of life, assess by EQ-5D.[3, 4]

Not surprisingly, the adverse event in cannabis extract was high as 80 %. This data was similar to the previous study, which the rate of any adverse event as high as 93 %[3, 7] in the cannabis trial active arm. However, the side effect is usually mild with a common problem such as a dry mouth, hypersomnolence, dizziness. Besides, the discontinuation rate in our study is 20 % caused by hyperemesis syndrome. Compare to other discontinuation rates in cannabis, extraction studies due to an adverse event were varied from 3-21%.[3-5, 7]

This study was the first study to report the efficacy of GPOCE in the treatment of spasticity in patients with MS. However, the small sample size was enrolled. The benefit of GPOCE produces in Thailand to treat spasticity in MS both objective and subjective aspect was observed. This finding of both efficacy and side effect suggest GPOCE probably has the characteristic similar to Nabiximol, which is the approved drug produce by GW pharmaceutical company, nevertheless the price of GPOCE cheaper than Nabiximol around one-tenth. Thus, cannabis extract produce under Thai pharmaceutical companies might play an essential role in treating spasticity of patients with MS not only in Thailand but also in low and middle-income countries.

There were several limitations to our study. This study is only a small number of patients' lack of control. Treating physicians and outcome assessment were the same person that causes response bias, which can explain the efficacy of medication was higher compared to the previous study (80% vs. 35-40%). Moreover, this study was enrolled patients during the Covid-19 pandemic, so only the small number of patients voluntarily in this clinical study. Further studies randomized, double-blind control trial of GPOCE should be performed to prove the efficacy and safety of this medication.

Conclusion

GPOCE is effective in treat spasticity in a patient with MS. The safety profile is acceptable under the supervision of the health care provider. The price of this product lower than current approve cannabis form GW pharmaceutical company, Nabiximol, might provide benefits for patients with MS in Thailand and other low to a middle-income countries.

What is already known on this topic?

Spasticity is one of the most common symptoms that affect patients' quality of life in patients living with MS. Most of the patients didn't respond to the current anti-spastic drug. The cannabis has been proved to relieve spasticity in MS in various clinical studies and support by the meta-analysis. However, the price of approved cannabis extraction to treat spasticity, namely Nabiximols, is relatively high, approximately 20,000-30,000 Thai baht (THB) per month. This study investigates the effect of Government Pharmaceutical

Organization cannabis extraction (GPOCE) to evaluate the efficacy and safety of GPO oral cannabis extraction in the treatment of spasticity of MS patients in Thailand.

What this study adds?

GPO cannabis extract is effective in treat spasticity in a patient with MS. The safety profile is acceptable under the supervision of the health care provider. The price of this product lower than current approve cannabis form GW pharmaceutical company, Nabiximol, might provide benefits for patients with MS in Thailand and other low to a middle-income countries.

Conflict of interest

The authors declare no financial or other conflicts of interest.

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