ISSN: 2639-0221

Gratis

Case Report

Journal of Pharmaceutics and Therapeutics

Cannabinoid Microdosing Improve Spasticity in a Traumatic Brain Injury Patient: A Case Study

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Received date: Jul 31, 2019; Accepted date: Sep 18, 2019; Published date: Sep 25, 2019

Abstract

A twenty-seven year old woman who suffered a severe traumatic brain injury (TBI) 10 years ago is the patient of this study. She has had a generalized spasticity on the right side presenting between 40 and 50 spasm crises by day, as well as cognition deficit, increased tonus and stiffness. Thus, our objective was to evaluate the therapeutics effects of a cannabis extract on this clinical condition. The clinical evaluation points were at days 7, 14, 45, 75, 105, 135 and 165. Spasms crises were evaluated 15 days before the treatment and 15 days after the start of treatment. Patient received microdose of cannabinoids for six months. The initial dose was around 170 µg of THC and 28 µg of CBD, dropping to 52 µg of THC and 7 µg of CBD by the end of treatment. The treatment reduced number of spasm, muscle tone, hyperreflexia and stiffness. Further, this treatment improved her cognition, short-term memory, speech, sense of humor, sleep and quality of life globally. This study shows for the first time that a very low dose of THC/CBD, in the order of micrograms, presented therapeutic effect in a human. Also, the ratio 6:1 between THC and CBD of this treatment is a new and interesting data to support new researches including cannabinoids and spastic syndrome.

Keywords: THC, Trauma brain injury, CBD, Spasticity, Microdose

Abbreviations: BDNF: Brain Derived Neurotrophic Factor; CB1: Cannabinoid receptor 1; CB2: Cannabinoid receptor 2; CBD: Cannabidiol; HADS: Hospital Anxiety and Depression Scale; HPLC: High Performance Liquid Chromatography; MS: Multiple Sclerosis; TBI: Traumatic Brain Injury; THC: Tetrahydrocannabinol

Introduction

Spasticity is defined as a set of involuntary muscle hyperactivity, which consists of *sensu strictu* spasticity, stiffness, dystonia or spasm or a mixture of these. This muscular hyperactivity is related to different etiologies and its complications are strong contractures and pain [1]. For instance, spasticity can be a primary symptom of multiple sclerosis (MS), or induced by traumatic brain injury (TBI). When spasticity is a consequence of MS, there is a lesion of the myelin sheath, caused by immune mediated destruction of oligodendrocytes from the white motor fibers (axon of the superior motor neuron). While, when spasticity is induced by TBI, there is a cortical lesion at the level of the upper motor neuron cellular bodies [2-4].

Pharmacological and surgical options to treat spasticity are available, but there is no consensus among experts regarding which one is the best option as a primary standard. Therefore, the type of treatment is generally decided on a case by case basis, making

this a controversial issue, due to the wide variation of how patients respond to each treatment [5]. Current pharmacological treatments usually have low efficacy, require high doses and often induce considerable side effects. Examples of usual treatments for spasticity are baclofen, gabapentin, pregabalin, diazepam, dantrolene and tizanidine [6]. Botulinum toxin presents good effectiveness for stiffness and spasm, but it does not present the same result for *sensu strictu* spasms [1].

In recent years, the *Cannabis*-based product Sativex has come to the market as an interesting novel resource for the neurologists and patients. Sativex is composed by cannabinoids, mainly tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio, with 27 mg/ml of THC and 25 mg/ml of CBD. It is administered as an oromucosal spray with clinical indication for MS-induced spasms [7-14]. Sativex has been shown to improve spasms, hypertonia, stiffness, hyperreflexia and pain in MS patients. It also improves patient's quality of life and presents mild side effects, such as somnolence, nausea, diarrhea and anxiety that can usually be reduced by titration dose [11,13-16]. Although the antispasmodic mechanism of Sativex is not yet fully elucidated, this effect is associated to the THC-induced activation of the CB1 cannabinoid receptors [14,17,18], which is consistent with data gathered in animal models of spasticity [19].

THC and CBD are the two most studied biological active phytocannabinoids from the *Cannabis* plant. THC, besides acts mainly through direct activation of cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), appears to be epigenetically related by histone acetylation in synaptogenic mechanisms [20]. CBD has multiple mechanisms of action, including enhancement of endocannabinoid levels, allosteric inhibition of CB1 receptors internalization [21], allosteric modulation of CB2 receptors [22] and even off-target receptors in the adenosinergic and serotoninergic systems [23,24]. CBD can antagonize some undesirable effects of THC, such as intoxication, sedation and tachycardia, while contributes to analgesic, antiemetic and anticarcinogenic THC properties [17]. Therefore, treatments with combined THC/CBD products tend to be more tolerated and effective than pure THC or CBD [25,26].

Regarding cannabinoid doses, although there are no studies evaluating cannabinoids microdoses in humans, some *in vitro* and *in vivo* studies have suggested this potential [20,27-31]. It has been shown that THC can activate cannabinoid receptors with a nano and micromolar range dose [27,28] and also it can induce biochemical and behavior changes in animals with very low doses [20,27-31].

Despite cannabinoids effective results on spastic syndrome induced by MS, these drugs have not yet been evaluated on spastic syndrome induced by TBI. It is important to mention that, although, the spastic syndrome has distinct etiologies when induced by MS or TBI, both are consequence of primary motor neuron lesion [2-4].

Our hypothesis was that microdoses of THC/CBD may cause clinical improvement in spastic syndrome from TBI, including reducing the number of spasms. Therefore, our objective was to describe the clinical effects of a microdose *Cannabis* extract (THC/CBD) experienced by the patient mentioned in this study.

Case Presentation

The patient

The patient of our study is a 27 years old, woman, who has a history of severe traumatic brain injury (TBI) due to a car accident 10 years ago. The accident left the patient with an after-effect of generalized spasticity, which is more accentuated on the right side. At first visit, she presented partial dependence to perform daily activities. The neurological examination pointed out the classic clinical signs of the spastic syndrome: increased tonus, stiffness and medial torsions in the muscles of the upper and lower limbs (especially elbow, wrist and ankle joints), contributing to her dysfunctional gait (Wernicke-Mann posture).

She had between 40 and 50 spasm crises per day on average, containing mild and severe spasms, with strength limitation of limbs, pain and increased resistance to mobilization in joints (mainly on the right side). Also, she had hyperreflexia of the physiological reflexes (patellar, aquilles, biceps, triceps) and pathological reflexes presented bilaterally (Tromner, Hoffman and Babinski). During the clinical examination, it was noticeable that she had language dysfunction, dysarthria and difficulty to understand complex sentences.

Quantification of cannabinoid compounds in the product

The quantification of cannabinoids present in the *Cannabis* extract was performed via a standard method using high performance liquid chromatography (HPLC) with a diode-array UV-VIS detector (DAD), adapted

from [32]. The methods used here are described in the analytical monograph from the Office of Medicinal *Cannabis* (Netherlands) and were already used in peer-reviewed publications [33].

Treatment history and general procedures

Firstly, we counted the number of patient spasms for 15 days before the beginning of the treatment. The patient took the treatment at home, helped by her caregiver, and came twice in the first month and once in the following months to be evaluated by a neurologist from our team. The current follow-up period of this patient is 6 months. She started taking 10 drops once per day for 1 month, following the maximum suggested dose in the product label. As the results were good, objectifying evaluate the effective level dose, we reduced the doses to 6 drops in the next month and to 3 drops in the last 3 months of her treatment.

Evaluation of spasticity, spasms and pain

The clinical evaluation of spastic syndrome was performed by examinations on the right and left hemisphere limbs using the Modified Ashworth Scale and Pen spasm scale [3,34]. The evaluations occurred one day before the beginning of treatment (T0) and on days 7, 14, 45, 75, 105, 135 and 165 henceforth called T1, T2, T3, T4, T5, T6 and T7, respectively. The number of spasms crisis of the right upper limb was evaluated for 15 days prior to treatment (-15 to 0 day) and 15 days after the beginning of treatment (0 to 15th day). The spasms were classified by intensity (mild and severe), and counted daily by the caregiver. The patient pain level was assessed by the visual analogue scale of pain application [35].

Evaluation of cognitive improvements

When we planned the design study, the cognition evaluation was not included in our objective list. However, after some weeks we clearly noted the beginning of some patient cognition improvements. Then, we systematized cognition parameters collecting data from our clinical observations and from the caregiver reports.

Evaluation of side effects

Anxiety and depression scores were evaluated using the Brazilian Portuguese validated Hospital Anxiety and Depression Scale (HADS) questionnaire [36] for the primary purpose of verifying any potential side effect. Further, in all time points evaluation (T0 to T7) the patient was encouraged by our team to relate any possible side effect.

Results

Quantification of cannabinoid compounds in the product

The concentrations in the sample were obtained by extrapolation from the areas under the curve for each identifiable peak of the chromatograms with the aid of standard curves using reference standard material for each analyte, as shown in Figure 1. The estimated concentration in the product (weight/volume) is below 1% for any of the main cannabinoids we tested (CBD, THC, CBG, CBC, THCA, CBDA and CBN) and below the detection limit for any cannabinoid other than THC and CBD. The only identifiable peaks of cannabinoid molecules were THC (RT 6.95) and CBD (RT 3.52).

An unknown molecule was detected at RT 9.6 which one we consider very improbable to induce any pharmacological effect due to its negligible concentrations. CBD was present in the sample at the very low concentration of 0.006% and THC was present at a concentration of 0.035%.

Extrapolating from the amounts taken by the patient along the treatment period and based on the extract concentration of THC/CBD, we estimate that the patient initiated treatment with 170/28 µg of THC/CBD (equivalent to 10 drops, around 500 µl orally) in the 1st month, reduced to 100/17 µg of THC/CBD in the 2nd month (6 drops, around 300 µl orally) and ended up taking only 52/9 µg of THC/CBD per day (3 drops, around 150 µl orally) during the last 4 months of treatment. Either of these doses is extremely low, and to the best of our knowledge, this is the first report of clinically-relevant effects of cannabinoid compounds in this dose range.

Spasms, spasticity and pain

The patient presented a marked reduction in the number of spasms over the course of the treatment. The number of spasms before the treatment and after the initiation of the treatment, was significantly different ($p < 0.001$, Student's T test). After the 15th day of treatment until the end of the study the number of spasms crisis was never higher than 2 per day. Number of mild (A) and severe spasms (B) in the right upper limbs observed for 15 days before the treatment and for 15 days after the beginning of the treatment. In panel A the mean and the standard error of the median (SEM) of the pre-treatment and post-treatment period was 23.13 ± 1.22 and 10.40 ±

2.20, respectively. In panel B the mean and the SEM of the pre-treatment and post-treatment period was 20.67 ± 0.99 and 7.27 ± 2.24, respectively (Figure 2).

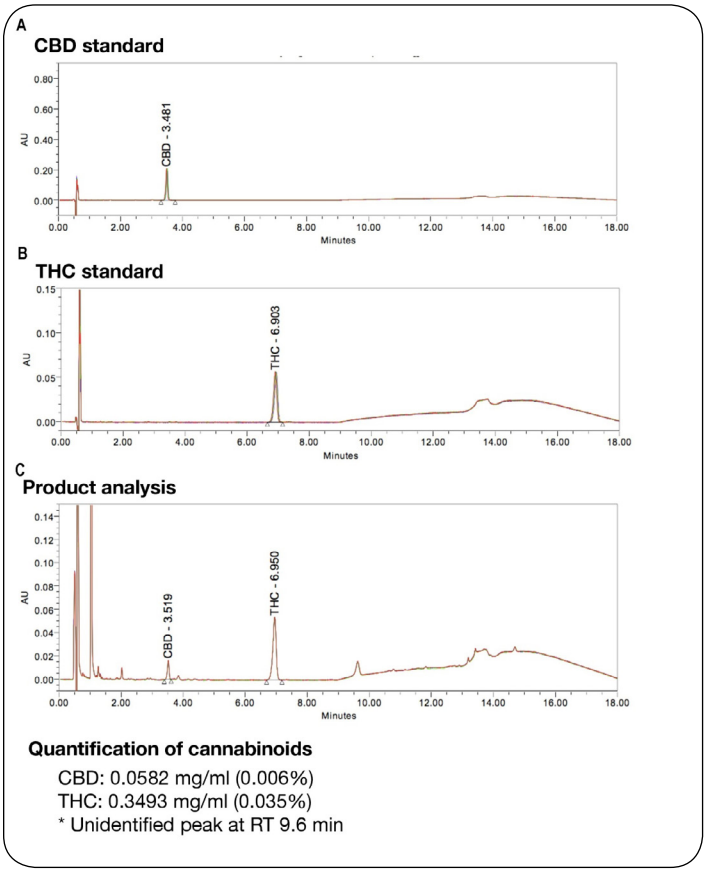

Figure 1: Chemical analysis of the THC-rich cannabis extract.

In general, the treatment induced a remarkable improvement in spasticity, including tonus, stiffness, spasms, physiological and pathological reflexes, motor and daily activities. These improvements resulted in an enhancement in her functional independence and in a substantial improvement in her quality of life.

As shown in Table 1, the *Cannabis* extract also substantially reduced the most signals and symptoms induced by spastic syndrome according to the Modified Ashworth Scale. In addition, the treatment induced a marked reduction of the spasms on Peen scale on right upper limb. At T0 the patient presented mild spastic hypertonia in the left hemibody, which was also reduced by treatment. It was also observed a reduction in the physiological reflexes of the upper and lower limbs that were previously exacerbated. The pathological reflexes of Trommer and Babinski remained present during the study, except the Babinski reflex that was absent at T6 clinical examination.

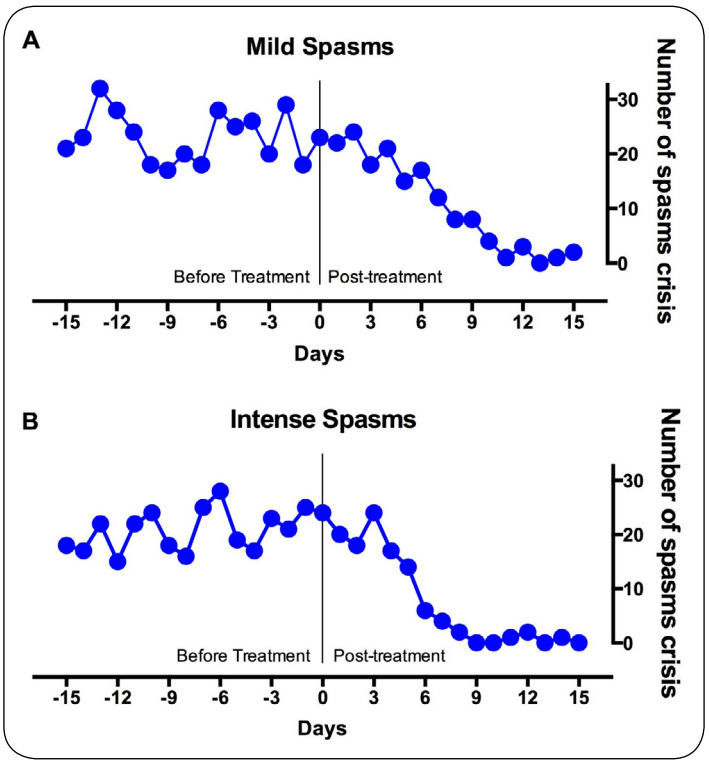

Figure 2: Antispasmodic activity of a microdose of THC-rich cannabis extract.

In addition, the treatment induced significant improvements regarding her dysarthria, gait, ability to get on and off the stretcher, ability to remove and wear the shoes. According to the caregiver's report (in a free translation to English): "...she presented significant improvement in activities, such as dressing on her own, moving around the house easily, using the right side to feed herself independently, applying makeup on herself and writing. She is getting autonomy in her daily activities"...

Regarding the pain levels, the patient did not report spontaneous spasmodic pain at T0, although she used to present a light pain during the neurological exam mobilizations. A discrete reduction in the level of pain induced by the mobilizations performed in the limbs during the neurological physical examination was verified. We suggest that this pain improvement was induced by tonus and stiffness reduction.

Cognitive improvements and side effects

After some weeks, we clearly noted the beginning of some improvement on patient's cognition. The improvement of the patient cognitive skills was remarkable, especially after the third week of treatment.

Table 1: Clinical analysis of spasticity and related signals.

Right Upper Limb	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**
Tonus	4	3	1+	0	1	1	1	1
Spasms	4	3	1	1	1	1	1	no
Reflexes	hyperreflexia of biceps, radial and palmar	hyperreflexia of biceps, radial and palmar	hyperreflexia of biceps	hyperreflexia of biceps	All reflexes are normal	hyperreflexia of radial	hyperreflexia of biceps and radial	hyperreflexia of biceps and radial
Pathological reflex (Tromner)	yes	yes	yes	yes	yes	yes	yes	no
Pathological reflexes (Hoffman)	yes	yes	yes	yes	yes	yes	yes	yes
Joint stiffness	† † †	† †	†	no	†	†	†	†
Degree of Strength	3	3	3	4	4	3	3	4
Right Lower Limb	T0	T1	T2	T3	T4	T5	T6	T7
Tonus	3	2	1+	1+	1+	1	1+	1
Spasms	No	No	No	No	No	No	No	No
Reflexes	hyperreflexia of Achilles and patellar	hyperreflexia of Achilles	All reflexes are normal	hyperreflexia of Achilles	All reflexes are normal	hyperreflexia of Achilles and patellar	hyperreflexia of Achilles and patellar	All reflexes are normal
Pathological reflexes (Babinski signal)	yes	yes	yes	yes	yes	yes	no	yes
Joint stiffness	† †	†	†	†	†	†	†	†
Degree of Strength	3	3	4	4	4	4	4	4
Left Upper Limb	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**
Tonus	1+	1	0	0	0	0	0	0
Spasms	no	no	no	no	no	no	no	no
Reflexes	hyperreflexia of triceps and biceps	hyperreflexia of triceps and biceps	hyperreflexia of triceps and biceps	hyperreflexia of triceps and biceps	hyperreflex-ia of biceps, radial and palmar	hyperreflexia of triceps, biceps and radial	hyperreflexia of triceps, biceps, radial and palmar	hyperreflexia of triceps, biceps, radial and palmar
Pathological reflex (Tromner)	yes	yes	yes	yes	yes	yes	no	no
Pathological reflex (Hoffman)	yes	yes	yes	yes	yes	yes	yes	yes
Joint stiffness	†	†	no	no	no	no	no	no
Degree of Strength	4	4	4	4	4	4	4	4
Left Lower Limb	T0	T1	T2	T3	T4	T5	T6	T7
Tonus	1	1	1	1	1/0	2/1.	1/0	0
Spasms	no	no	no	no	no	no	no	no
Reflexes	hyperreflexia of Achilles and patellar	hyperreflexia of Achilles	All reflexes are normal	hyperreflexia of Achilles	hyperre-flexia of Achilles	All reflexes are normal	All reflexes are normal	hyperreflexia of Achilles
Pathological reflex (Babinski signal)	yes	yes	yes	yes	yes	yes	no	yes
Joint stiffness	†	†	†	†	†	†	no	†
Degree of Strength	4	4	4	4	4	4	4	4

Tonus was evaluated according to Modified Ashworth Scale (from 0 to 4). Spasms was evaluated according to Peen scale (from 0 to 4). Legend of the signals: † † † (intense); † † (moderate); † (light).

This became clearly noticeable when she was answering the HADS questionnaire. Until the T0, T1 and T2, she could not answer the questionnaire by herself because of her neurologic condition. However, she surprised us at T3, when she spontaneously took the sheets and answered the questionnaire by herself, with no need of the researcher's supervision or instructions. After that, we decided to systematize the data collection of cognition parameters, including our clinical observations and reports from the caregiver.

According to the information shown on Table 2, the patient presented improvements in text interpretation, thought, cognitive processing to choose an answer (questionnaire), fine motor coordination and ability to understand and elaborate sentences and speech. In addition, the patient presented improvement in her ability to communicate in oral and written language (also observed during our interviews and clinical examinations).

Regarding effects of this treatment on patient's memory, in an interview without the patient presence, the caregiver reported that the patient recovered old memories (in an English free translation): "...*she remembered events that occurred immediately before (a couple of months) the car accident which had induced her condition. These memories had been completely forgotten and were never mentioned by her after the accident*". This kind of reports were already cited in the literature by *Cannabis* non-medicinal users [37].

The caregiver also reported that the patient presented a considerable increase in short-term memory after the treatment: "... before the treatment, when she asked me for ice cream, I used to say that I would buy it on the next day and, at the next day, she usually did not remember my promise anymore. Now, whenever I promise ice cream, the day after, she remembers and demands me to fulfil the promise". Although these improvements were not analyzed by objective clinical protocols, they strongly corroborate to the patient's clinical history.

Table 2: Observation of the evolution of cognition skills.

Cognition reports	T0/T1	T2	T3	T4	T5	T6	T7
Answering the HADS Questionnaire	She barely understands the questions. It is necessary to read and repeat the questions many times.	She does not understand well the questions. It is necessary to repeat the questions some times.	She does not understand well the questions. It is still necessary to repeat some questions.	She understands well the questionnaire. She barely holds the questionnaire and fill part of it very slowly.	She understands well the questionnaire. She holds the questionnaire and answer it by herself for the first time.	She understands well the questionnaire. She holds the questionnaire and answer it by herself.	She understands well the questionnaire. She holds the questionnaire and answer it by herself.
Pen use	During the questionnaire the researcher uses the pen to fill the questionnaire according to the patient answers	During the questionnaire the researcher uses the pen to fill the questionnaire according to the patient answers	During the questionnaire the researcher uses the pen to fill the questionnaire according to the patient answers	She holds the pen by the first time and fill part of the questionnaire.	She holds the pen and easily fill up all the questionnaire.	She holds the pen and easily fill up all the questionnaire.	She holds the pen and easily fill up all the questionnaire. Also, spontaneuouly the writes her name within a small space of the header by the first time.
Speech	Truncated, slow and barely comprehensible speech.	Truncated, slow and barely comprehensible speech.	The speech is less truncated and reasonably comprehensible.	The speech is continuous and reasonably comprehensible.	The speech is totally continuous and easily comprehensible.	The speech is totally continuous and easily comprehensible.	The speech is totally continuous and easily comprehensible.
Other reports	No other reports	Patient reports improvement of quality of sleep and a "morning hapiness"	No other reports	Improved memory of everyday things	Improved memory of everyday things	She begins to read a book by the first time after the TBI	She starts to feed by herself with the right hand
Observation of capacity of comprehension, fine motor activity, speech and other cognition skills of patient.							

Throughout the duration of the study, the only side effects observed were light diarrhea and some somnolence in the first week of treatment, according to the caregiver's description. After that, neither the patient nor her caregiver related any side effect. The occurrence of common side effects related to cannabinoid treatments like increase of appetite, dizziness or sleepiness was specifically asked at each clinical examination, but the answer was negative.

Additional reports from the caregiver were the absence of daily complaints of headaches and the improvement in the quality of sleep. The lack of any relevant side effect is easily explained by the cannabinoids very low doses used. Regarding the HADS questionnaire application, anxiety and depression scores were at subclinical levels at the baseline and they remained like until the end of treatment (data is not shown).

Discussion and Conclusion

In this study, the treatment of a spastic syndrome patient who received a microdose of a *Cannabis* extract presented the main highlights: i) THC/CBD microdosing (170/28 - 52/9 µg/day, p.o.) improved on patient's spastic symptoms, as well as cognition and quality of life; ii) the treatment used was devoid of any significant adverse effect, and iii) to the best of our knowledge, this is the first objective study in the scientific literature showing therapeutic effects of THC/CBD in a true microgram dose-range in human patients.

Although the etiology of the spastic syndrome of the patient evaluated in this case report is distinct from the spasms of the patients evaluated in most of the Sativex studies [8-14,38], it is interesting to comment that THC/CBD doses used here are several times lower than the usual ones. According to the manufacturer data, Sativex is a solution containing 27 mg/ml of THC and 25 mg/ml of CBD, i.e., a 1:1 ratio. Usually, Sativex patients use an average of 8 sprays per day, which is around 20 mg of each cannabinoid per day [12,39,40]. The product analyzed in this study contained only 0.35 mg/ml of THC and 0.06 mg/ml of CBD (Figure 2). At the first month of the treatment the patient received approximately 500 µl/day of product, containing less than 200 µg of THC and 6 times less CBD. This is over 100 times less drug in comparison to Sativex with noticeable evidence of efficacy.

Despite the obvious limitations of this study, the consistency of the clinical data over 6 months of treatment motivated us to report this clinical case. These results are important evidences suggesting by the first time that microdose of THC/CBD could indeed be used to treat spastic symptoms in humans and it deserve to be further investigated.

Although there is no clinical study showing that cannabinoids microdoses can induce therapeutic effects, some *in vitro* and *in vivo* studies support our data. Has been shown that THC is able to activate CB1 and CB2 receptors, within Ki values in the nano and micromolar concentration range [27,28,41]. Further, *in vivo* studies has demonstrated that very low and ultra low doses of THC, such as 0.002 mg/kg, induces improvement in memory, learning and cognitive parameters in mice [29-31,42,43]. Another study describes the effects of micromolar and nanomolar concentrations of THC and CBD at modulation of the mitogen-induced tryptophan degradation and neopterin formation in peripheral blood mononuclear cells, correlating these effects with the serotoninergic system and psychiatric disorders, like depression [28].

Our positive results on patient cognition with such a low dose of THC/CBD is a human evidence in support of recent animals studies showing that low doses of THC improves memory and restores synaptogenesis in rats [20,27-31,42,43]. Although there are studies trying to make clear the relationship between neurotoxic and neuroprotective effects and high or low doses of cannabinoids [44], we think that this may be more complex and unpredictable. Regarding THC, its neuroprotective effects seem to be related to the production of neurotrophins, such as brain derived neurotrophic factor (BDNF), axonal and synaptic proteins, as well as the reduction of inflammatory factors and inflammatory responses that lead to neuronal death [20,27-31,42,43].

The range cannabinoid dose used here is in line with previous evidence, showing that THC begins to present substantial psychoactive effects at oral doses starting from 30 mg, which is around 200 times over the dose reported here. Moreover, severe addictive effects such as irritability, mood and sleep alterations have only been reported in chronic heavy users at doses above 150 mg/day [45]. The results here reported yielded the hypothesis that microdoses of THC/CBD are clinically effective for human patients with neurological disorders. Further, according to our observation and previous clinical data, we believe that this dose range is absolutely safe. At least, there is no reason to believe that *Cannabis* induces any of its typical effects at the microdose range.

In conclusion, this study shows that a microdose of THC/CBD in a 6:1 ratio can be a potential treatment to spastic syndrome induced by TBI. This range of dosage seems to be able to improve cognitive deficit and quality of life globally. Further, this microdose of THC/CBD does not induce any significant side effects.

Finally, extrapolating the results found in this case study and based on many animal studies, we hypothesize that doses of cannabinoids, mainly THC, in microdose range, can be therapeutically effective in humans and, in the near future, will open a great avenue on cannabinoid clinical studies.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the recommendations of Resolution N° 466 of the Brazilian Health Ministry. The protocol was approved by the Ethical Committee of Research – UNIOESTE University, by protocol number 82975518.6.0000.0107.

Consent for publication

The mother of the patient (caregiver) has given written informed consent in accordance with the Declaration of Helsinki for the publication of this case study.

Availability of data and material

All original results are available under request.

Competing interests

At the time of data collection, FAP and CGL worked for Entourage PhytoLab, a pharmaceutical start-up dedicated to the development of *Cannabis*-based medical products. The company allowed the use of the HPLC equipment, but had no further influence in the study, nor was the study carried out as a demand of the company.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. RMC holds a PIBIC/UNILA undergraduate scholarship.

Authors' contributions

RMC, EGS and FPN planned the experiments and evaluations. RMC, FAP, CGL, EGS and FPN performed experiments and analysed the data. RMC, FAP and FPN prepared the figures and tables. All authors wrote and approved the final manuscript.

Acknowledgements

We thank very much the patient of this study and her caregiver. RMC holds a PIBIC/UNILA undergraduate scholarship.

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