Complementary Therapies in Medicine 34 (2017) 170–185

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Cannabinoids for spasticity due to multiple sclerosis or paraplegia: A systematic review and meta-analysis of randomized clinical trials

Victoria P. da Rovare[a], Gabriel P.A. Magalhães[a], Guilherme D.A. Jardini[a], Matheus L. Beraldo[a], Mariel O. Gameiro[a], Arnav Agarwal[b,c], Gustavo José Luvizutto[d], Lucas Paula-Ramos[e,*], Samira Esteves Afonso Camargo[e], Luciane Dias de Oliveira[e], Rodrigo Bazan[d], Regina El Dib[e,f,g]

[a] São Paulo State University (Unesp), Botucatu Medical School, São Paulo, Brazil
[b] Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada
[c] Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[d] São Paulo State University (Unesp), Department of Neurology, Botucatu Medical School, Brazil
[e] São Paulo State University (Unesp), Department of Biosciences and Oral Diagnosis, Institute of Science and Technology, São Paulo, Brazil
[f] São Paulo State University (Unesp), Department of Anesthesiology, São Paulo, Brazil
[g] McMaster Institute of Urology, McMaster University, St. Joseph's Healthcare, Hamilton, Canada

ARTICLE INFO

Key-words:
Cannabinoids
Spasticity
Multiple sclerosis
Paraplegia

ABSTRACT

Objectives: Spasticity remains highly prevalent in patients with spinal cord injury and multiple sclerosis. To summarize the effects of cannabinoids compared with usual care, placebo for spasticity due to multiple sclerosis (MS) or paraplegia.

Methods: Searches of MEDLINE, EMBASE, CENTRAL and LILACS to March 2017 were performed to identify randomized controlled trials. The primary outcomes were spasticity and spasm frequency. The criteria were any patient with MS and spasticity affecting upper or lower limbs or both, and that had a confirmed diagnosis of MS based on validated criteria, or however defined by the authors of the included studies.

Results: 16 trials including 2597 patients were eligible. Moderate-certainty evidence suggested a non-statistically significant decrease in spasticity (standardized mean difference (SMD) 0.36 [confidential interval (CI) 95% −0.17 to 0.88; p = 0.18; I2 = 88%]), and spasm frequency (SMD 0.04 [CI 95% −0.15 to 0.22]). There was an increase in adverse events such as dizziness (risk ratio (RR) 3.45 [CI 95% 2.71–4.4; p = 0.20; I2 = 23%]), somnolence (RR 2.9 [CI 95% 1.98–4.23; p = 0.77; I2 = 0%]), and nausea (RR 2.25 [CI 95% 1.62–3.13; p = 0.83; I2 = 0%]).

Conclusions: There is moderate certainty evidence regarding the impact of cannabinoids in spasticity (average 0.36 more spasticity; 0.17 fewer to 0.88 more) due to multiple sclerosis or paraplegia, and in adverse events such as dizziness (419 more dizziness/1000 over 19 weeks), somnolence (127 more somnolence/1000 over 19 weeks), and nausea (125 more somnolence/1000 over 19 weeks).

1. Introduction

Spasticity can be considered disabling when it involves severe functional problems, and the management is essential to prevent further deterioration in function. If not managed in a timely manner, spasticity can lead to diminished activity, and problems with daily living activities (ADL) such as gait, feeding, washing, dressing and toileting.[1] Over time, spasticity may cause muscle pain, stiffness or spasms, trouble moving, impaired ability to stand and walk, difficulty eating and speaking, contracture leading to joint and bony deformity and even incontinence episodes [2]

Spasticity remains highly prevalent in patients with spinal cord injury (SCI) and multiple sclerosis (MS). In SCI patients, the lesion of the neurons in the spinal cord results in upper motor neuron syndrome with a prevalence of 65% to 78% in the first year post-injury,[3] and in MS, the same is caused by the demyelination of nerve fibers of spinal cord and is present in 84% of North American cases.[4]

The treatment of multiple sclerosis has changed over the last years.

* Corresponding author at: Regina El Dib, Department of Biosciences and Oral Diagnosis, São Paulo State University (Unesp), Institute of Science and Technology, São José dos Campos, Francisco José Longo 777, São Dimas, São José dos Campos, SP, 12245-000, Brazil.

E-mail addresses: victoriarovare@gmail.com (V.P. da Rovare), beelz.magalhaes@gmail.com (G.P.A. Magalhães), guilhermejardini@gmail.com (G.D.A. Jardini), beraldoa@hotmail.com (M.L. Beraldo), marielorsi@gmail.com (M.O. Gameiro), arnav.mcmaster@gmail.com (A. Agarwal), gustavo.luvizutto@uftm.edu.br (G.J. Luvizutto), lucas93paula@hotmail.com.br (L. Paula-Ramos), samira@ict.unesp.br (S.E.A. Camargo), luciane@ict.unesp.br (L.D. de Oliveira), bazan.r@terra.com.br (R. Bazan), eldib@fmb.unesp.br (R. El Dib).

http://dx.doi.org/10.1016/j.ctim.2017.08.010
Received 5 July 2017; Received in revised form 4 August 2017; Accepted 16 August 2017
Available online 26 August 2017

The existing options for the treatment of spasticity, such as baclofen, tizanidine, benzodiazepines, morphine, and botulinum toxin present great limitations requiring frequent administration of high doses, often causing incapacitating side effects, and having a large number of patients who are unresponsive to therapy.[5] Overall, the treatment of MS comprises three main groups: i) treatment of the acute attack; ii) prevention of future attacks by reducing triggers and use of disease-modifying therapies; and iii) symptomatic treatments of neurological difficulties such as spasticity, pain, fatigue, and bladder dysfunction. Thus, there is an urge for new treatment approaches, represented in the last decade by a number of publications regarding the use of cannabinoids and their effect in the endocannabinoid system.

The endogenous cannabinoids anandamide, 2-arachidonyl glycerol (2-AG) acts on specific cannabinoid receptors: CB1 receptors, present mostly in the CNS; and CB2 receptors, located in the CNS and extensively in the periphery (specially the immune system).[6] Cannabis sativa L. contains 60 or more cannabinoids, the most abundant of which are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[6] THC is a partial CB1 receptor agonist providing analgesia, muscle relaxation, anti-emesis, appetite stimulation and psychoactivity.[6] CBD has anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, antioxidant and antipsychotic activity and has been shown to reduce the anxiogenic and psychoactive effects of THC.[6] Both endogenous and exogenous cannabinoids have been shown to have an anti-spasticity effect in the recognized animal model of MS spasticity, and treatments that include THC and CBD have great potential for treating spasticity both in MS and SCI.[6]

There are a variety of new medications yet to be approved by governments that explore the effects of cannabinoids in the treatment of cancer pain, neuropathic pain, epilepsy, metabolic syndrome, inflammation, psychiatric disorders, spasticity in multiple sclerosis and spinal cord injury and other conditions, not to mention the possibility of using in-natura plant extracts.[7]

A recent systematic review of 79 trials addressing patient-important outcomes and including over 6000 patients reported that cannabinoids was associated with a reduction in spasticity as well as with improvements in nausea and vomiting due to chemotherapy, and weight gain in HIV infection, sleep disorders, and Tourette syndrome.[8] A more specific meta-analysis on chronic pain and psychiatric problems concluded that there is high-quality evidence supporting the use of marijuana or cannabinoids.[9]

We therefore undertook a systematic review of all randomized controlled trials (RCTs) comparing any type of cannabis extract or cannabinoid-based medication with usual care or placebo focusing on patient-important outcomes for multiple sclerosis and spinal cord injury patients with spasticity. The aim of this systematic review and meta-analysis is to look into more detail on the use of cannabinoids for these particular conditions. The intent to highlight specifically spasticity is due to the recent regulation of 1:1 THC:CBD oromucosal spray as a prescription medication in Brazil for patients with multiple sclerosis resistant to the current existing treatment.

2. Methods

The Cochrane Handbook for Intervention Reviews.[10] guided our choice of methods. This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement [11] and, the Quality of Reporting of Meta-analyses QUOROM [12]

2.1. Eligibility criteria

- Study design: RCTs.
- Participants: patients with spasticity due to MS or paraplegia (i.e. complications of paralysis of the legs and lower parts of the body) affecting upper or lower limbs or both, and that had a confirmed diagnosis of MS based on validated criteria, or however defined by the authors of the included studies, and regardless the subgroup of the disease such as relapsing remitting, primary progressive and secondary progressive MS.
- Interventions: cannabis plant, with any compounds such as delta-9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD), regardless the type of extracts (e.g. oil, hash, tinctures).
- Comparators: usual care, placebo or no intervention.
- Patient-important outcomes: the primary outcomes were spasticity, and spasm frequency and severity. Secondary outcomes were pain measured by any validated scale, bladder function; cognitive function; ADLs; and occurrence of any adverse events (dizziness, somnolence, nausea, dry mouth).

Eligible studies followed patients for a minimum of two weeks. We did not consider studies reported as conference abstracts due to the lack of complete information they contained.

2.2. Data source and searches

A previous review.[8] with similar inclusion criteria identified studies using cannabinoid treatment for different outcomes up to April 2015. We selected from the previous review [8] only the RCTs that analyses the use of cannabis-based medication for spasticity, and developed a search strategy (Appendix Figure A1) for MEDLINE, EMBASE, Cochrane Controlled Trials Register (CENTRAL) and LILACS up to March 20, 2017. The review authors scrutinised the reference lists of the identified relevant studies for additional citations. We consulted clinical specialists and contacted authors of included trials where appropriate to obtain unpublished data.

2.3. Selection of studies

After identifying all potentially eligible studies by the literature search and obtaining all of their full-text articles, teams of two reviewers independently evaluated these studies for eligibility. Disagreements were resolved through discussion with third party adjudication. We calculated the agreement, using kappa statistic, between reviewers for full-text screening.

2.4. Data extraction and risk of bias assessment

The following data were extracted independently by three pairs of reviewers using a pre-standardized form that included characteristics of the study design, participants, interventions, outcomes event rates and follow-up. Authors of the eligible studies were contacted by reviewers to identify missing data and confirm data accuracy. As there was multiple publication of the same study, we decided to quote all these references under results section.

The pairs of reviewers assessed risk of bias separately by using a modified version of the Cochrane Collaboration's tool [13] which includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the previously cited domains [14] A low risk of bias was designated for incomplete outcome data, loss to follow-up of less than 10% and a difference of less than 5% in missing data in intervention and control groups. If needed, reviewers discussed with a third party adjudication to resolve disagreements.

2.5. Certainty of evidence

Reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for certainty of evidence. Each outcome was rated high, moderate, low, or very low.[14] Detailed GRADE guidance was used to evaluate overall risk of bias,[15] imprecision,[16] inconsistency,[17] indirectness,[18] and publication bias [19] and results were summarized in an evidence profile.