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Research Article

Topical Magnesium-Coordinated Cannabidiolic Acid (CBDA) for the Treatment of Restless Leg Syndrome

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ABSTRACT

Topical Magnesium-Coordinated Cannabidiolic Acid (CBDA) for the Treatment of Restless Leg Syndrome Restless Leg Syndrome (RLS) is multifactorial disease state with many different potential pathophysiological mechanisms, which includes iron deficiency, dysfunctions from the cerebral cortex and spinal cord to mechanosensitive channels at the musculoskeletal periphery. Most therapeutic agents effectiveness focuses on the central nervous system (e.g., dopaminergic drugs) or Renshaw cells. There are virtually no effective therapeutic agents that are focused on the periphery. We hypothesize that treatment for RLS can focus on the peripheral musculoskeletal component of the disease, more specifically the mechanosensitive channels such as Piezo 2 and TRPA1. We conducted an open-label IRB-approved clinical trial using a proprietary topical preparation of our magnesium-coordinated CBDA to explore the responses to this novel treatment modality. We found a statistically and clinically significant improvement in restless leg symptoms and without any reported adverse effects.

Keywords: Restless leg syndrome; Cannabinoids; Cannabidiolic acid; CBDA; Insomnia; Mechanoreceptors

INTRODUCTION

Restless Leg Syndrome (RLS) is a neurological disorder characterized by an uncontrollable urge to move the legs, and discomfort. Symptoms typically occur during periods of rest, especially in the evening, causing significant sleep disturbances and daytime impairment. RLS can severely affect quality of life, impacting both physical and mental health. RLS affects about 5-10% of adults in the U.S., with a higher prevalence in older adults. Women are twice as likely as men to be affected [1]. Common treatments for RLS include medications such as dopamine agonists (e.g., pramipexole, ropinirole), anticonvulsants (e.g., gabapentin), and opioids. Iron supplements are recommended if iron deficiency is a factor. Untreated RLS can result in sleep disruption, fatigue, difficulty concentrating, and increased risk of anxiety and depression [2]. Our hypothesis focuses on treating the peripheral musculoskeletal component of RLS, particularly by targeting peripheral mechanosensitive channels. We present an open-label trial utilizing a proprietary topical magnesium-infused CBDA preparation, which demonstrated effectiveness with no adverse effects.

MATERIALS AND METHODS

Ten participants were enrolled, consented, and completed a Restless Leg Syndrome Rating Scale (RLS). They applied CBDA topical cream 30-45 minutes before bed, massaging the affected areas for 20 seconds, and reapplying if needed. Participants used the cream nightly for 14 days. Upon completion, participants were re-administered the RLS along with the Patient's Global Impression of Change (PGIC) questionnaire. Scores were interpreted according to their respective rubrics. Differences between baseline and post-intervention observations were tested for normality using Shapiro-Wilk tests. Parametric repeated-measures t-tests were used where normality assumptions were met. Statistical significance was set at an alpha value of 0.05 and analyses were conducted using SPSS Version 29. (Armonk, NY: IBM Corp.).

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RESULTS

Results of sample size of n=10 were analyzed. The first PGIC question had a median value of 6.50, with an interquartile range of 5.00-7.00. For the second question, the median value was 0.00 with an interquartile range of 0.00-1.00.

The difference score distributions for the RLS (p=0.33) and the RLS ordinal scale (p=0.36) both met the assumption of normality. There was a statistically significant decrease in RLS scores from baseline (M=25.80, SD=5.05) to post-intervention (M=8.00, SD=7.27), t(9)=6.58, p < 0.001, mean difference=17.80, 95% CI of the difference=11.68-23.92. There was also a statistically significant decrease in RLS ordinal ratings from baseline (M=5.20, SD=1.87) to post-intervention (M=1.40, SD=1.65), t(9)=5.88, p < 0.001, mean difference=3.80, 95% CI of the difference=2.34-5.26.

The participants had a pre-treatment average score with the RLS rating of 25.80 where a score between 1 and 10 is mild, 11 to 20 moderate, 21 to 30 severe, and 31 to 40 very severe RLS. After two weeks of treatment the average score was 8 with a p-value <0.001.

The RLS ordinal scale pre-treatment went from an average of 5.2 to a post-treatment score of 1.40 with a p-value < 0.001, with four participants claiming that they had no symptoms with the use of the topical CBDA cream.

PGIC revealed that participants' quality of life improved with the treatment, including improvement in sleep and improvement of daytime drowsiness (metrics measured with the RLS questionnaire).

The PGIC questionnaire revealed significant improvement, with an average score of 6.5 for the first question assessing quality of life indicators (on a 1-7 scale). The second question uses a 0-10 rating scale that examines the degree of change in symptoms since the start of the treatment. Zero is much better, 5 is no change and 10 is much worse. The average response to this question was less than 1.

The first RLS sleep question, how severe is your sleep disturbance, is rated 0-4 where 0=no symptoms and 4=very severe symptoms. The average pre-treatment score was 2.6 and at the completion of the trial the average score was a 0.4 with 6 participants reporting complete resolution of sleep disturbances.

The second RLS sleep-related question inquired about the severity of daytime sleepiness using the same 0-4 scale. The average pre-treatment score for the participants was 2.0 and the average post-treatment score was 0.3.

DISCUSSION

The use of topical CBDA cream demonstrated statistically and clinically significant improvement in RLS symptoms, including sleep disturbances and daytime tiredness. Importantly, no adverse effects were reported.

These promising results may be attributed to the unique formulation of the CBDA cream and its effects on enzymes (e.g., COX-2), receptors and ion channels (e.g., 5HT1A, TRPA1, Piezo 2, vanilloid). These physiological components are densely located in the dermis and epidermis, making them accessible for topical treatments. We hypothesize that magnesium-coordinated CBDA targets mechanosensitive channels like Piezo 2 channels and TRPA1 receptors, which are key to alleviating RLS symptoms.

Why piezo 2 channels and TRPA1 receptors?

Piezo 2 is considered the prime mechano-transducer. It is the main ion channel for mechanoreceptors and is responsible for detecting mechanical stimuli, such as stretch and pressure, and is crucial for proprioception and touch.

Proprioceptive dysregulation: Piezo 2 channels are essential for feedback on body position and limb movement. Dysregulated Piezo 2 activity could create abnormal sensations of restlessness or an "urge to move," core symptoms of RLS.

Abnormal mechanotransduction: Piezo 2 channels may contribute to the hyperactivation of stretch and pressure receptors in the muscles and joints. This hyper activation could trigger sensory discomfort, leading to the need for leg movement.

Link to movement relief: Movement alleviates RLS symptoms. Piezo 2's role in detecting mechanical changes during movement suggests it might modulate relief through the normalization of sensory input during activity. .

TRPA1 is a member of the transient receptor potential (TRP) channel family and is widely expressed in sensory neurons. It acts as a mechano-sensor and is activated by chemical and physical stimuli, including oxidative stress, inflammation, pain, and changes in mechanical forces.

Sensory hyperexcitability: TRPA1 receptors are associated with enhanced sensitivity to mechanical and thermal stimuli. Over-activation of these receptors may lead to the heightened sensory discomfort experienced in RLS.

Oxidative stress and inflammation: TRPA1 is activated by products of oxidative stress, which has been implicated in RLS. Inflammation and oxidative stress might amplify sensory neuron activation, contributing to the "crawling" or "tingling" sensations in the legs.

Peripheral-central crosstalk: Dysregulated TRPA1 activity in the periphery could send aberrant signals to the Central Nervous System (CNS), exacerbating the sensory and motor symptoms of RLS

We believe that magnesium-coordinated CBDA is modulating the membranes surrounding Piezo 2 channel gating due to the nature of the divalent ion and membrane integrity. Piezo 2 channels are regulated by the shape and rigidity of the surrounding membrane structure. Membrane tension is lessened with distortion of membrane structure, which is imparted by molecules that readily penetrate the membrane, such as amphiphilic molecules [3]. The magnesium-coordinated CBDA is formulated to be amphiphilic.

TRPA1 is an inherent mechanosensitive channel that, like the Piezo 2 channel, are gated by force-from-lipids. Lipophilic

compounds also act on TRPA1 by membrane bilayer perturbation, which impacts force amplification of Piezo 2 channel response to mechanical stimulation [4]. Our working hypothesis is that the amphiphilicity inherent in the magnesium-CBDA coordination complex, which incorporates the required lipophilicity, drives the membrane bilayer perturbation required for a modulated Piezo 2 channel response.

TRPA1 is also involved in the mechanism of action of RLS through oxidative stress, which can shape the response to mechanical stimuli by shifting TRPA1 into a force-to-lipid sensitive protein conformation. Moreover, the effect of non-electrophilic TRPA1 ligands may be indirect by changing the lipid tension stress on TRPA1 within the cell membrane [5].

An effective therapeutic agent to treat RLS targeted to the musculoskeletal periphery would be one that possesses: 1) effective amphiphilicity, 2) TRPA1 modulation and 3) divalent cations to interfere with the increased calcium flux initiated by overstimulation of Piezo 2 channels [6-8].

The magnesium-coordinated CBDA cream is designed to be both water-soluble and membrane-penetrating, enhancing its ability to pass through the epidermis to reach the dense expression of mechanoreceptors, receptors, and ion channels within the dermis. The deeper the penetration, the more receptors and ion channels are affected, leading to better symptom relief.

The trial had several limitations, including its small sample size and lack of a control group, suggesting the need for further research. Future studies should include a randomized, double-blind, placebo-controlled trial, as well as explore the potential of combining topical and systemic treatments. Additionally, laboratory experiments to investigate the mechanistic hypothesis of the cream's effects on mechanoreceptors would be valuable.

CONCLUSION

The proprietary magnesium-coordinated CBDA cream was used topically to treat RLS. The results revealed an interesting signal for a potentially safe and effective treatment for RLS. The primary and secondary endpoints were statistically and clinically significant improvements in RLS, and without any reported adverse effects. The trial suggests significant improvement in sleep disturbances and daytime sleepiness. This trial also suggests a novel and safe alternative treatment for individuals with RLS who have not found relief with traditional therapies.

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