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Efficacy and safety of topical 5% cannabidiol plus myrcene for the treatment of vestibulodynia: a randomized controlled trial

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Study Typology : randomized double blind, prospective trial

1. INTRODUCTION

Vulvodynia is a highly prevalent form of chronic genital pain in women, to such an extent that prevalence studies estimate ranges from 10% to 28% in reproductive-aged women. Localized provoked vulvodynia at the vestibule, known as vestibulodynia (VBD), is the most common manifestation of the disease (about 80%). Women with VBD often describe vulvar pain as a burning, stinging, irritation, rawness, and dyspareunia (difficult or painful intercourse). Most patients with VBD described their pain as "hot," "burning," or "pricking" and that the vestibular area is sensitive to the touch (e.g. during sexual intercourse or tampon use) and that the pain would be increased by rubbing.
The pattern of VBD responses is suggestive of sensory abnormalities in the form of evoked pain (e.g. hyperalgesia or allodynia), suggesting sensitization, an underlying manifestation of neuropathic pain. This is consistent with biopsy studies that have demonstrated increased innervation of the vulvar vestibule and an increase in subepithelial heparinase activity and cytokines that have been linked to neuroinflammatory processes; patients with VBD also experience body changes in sensitivity, suggesting that sensory dysregulation might be involved the expression of this pain condition. Furthermore, the discomfort inherent in VBD is always associated with pelvic floor muscle overactivity. This prolonged pattern can result in decreased tissue perfusion, muscle dysfunctional overactivity, and the development of myofascial trigger points, resulting in localized or radiating pain and/or intense tenderness. Neuropathic pain and hypertonicity can be considered a multifactorial and complex consequence of maladaptive neuronal plasticity. VBD is likely not one disease but rather several diseases, in which the common end point is vestibular hypersensitivity and pelvic floor hypertonic dysfunction. VBD represents a summation and overlapping of various trigger factors (infections, hormonal disturbances, allergies, genetic aspects, psychological vulnerability, and others) with weight and predominance varying from patient to patient. There is no standard treatment of the disease, and few randomized.
controlled trials have been performed, and the recommendations are in favor of a multi-dimensional treatment.

References

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2. STUDY OBJECTIVES

The Research Hypothesis for the present study is to prospectively document the efficacy and safety of the topical association cannabidiol (CBD) *plus* myrcene in patients with VBD. The abundant distribution of cannabinoid receptors on skin nerve fibers and mast cells provides implications for an anti-inflammatory, anti-nociceptive action of cannabinoid receptor agonists and suggests their putatively broad therapeutic potential. The non-psychoactive analog of tetrahydrocannabinol (THC), cannabidiol (CBD) has demonstrated significant analgesic, anti-inflammatory, anti-neuropathic activities without the psychoactive effect of THC. It was demonstrated that topical application of CBD can achieve significant improvement in pain and other disturbing sensations in patients with peripheral neuropathy. Myrcene (7-Methyl-3-methylene-1,6-octadiene) an acyclic monoterpene, is the most prevalent monoterpene in Cannabis. In preclinical studies, administration of essential oils rich in myrcene have been found to have analgesic and anti-inflammatory properties. We postulate that association of CBD plus myrcene could have a synergistic action on symptoms related to VBD.

3. DESCRIPTION OF RESEARCH DESIGN

3.1 Overall Study Plan
This is a randomized double blind, controlled trial.

3.2 Study Duration
Each eligible subject will participate in the study for approximately 2 months
It is expected this investigator-initiated research study will be completed approximately 6 months following initial approval by the Institutional Ethical Board.

3.3 Institutional Ethical Board Approval (IEB)
Prior to conducting any study-related procedures, the Principal Investigators will each obtain written approval from their respective IEB for the informed consent form, protocol, recruitment materials, and any written information provided to Subjects pertaining to the procedure.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

The study population will include women with VBD.

4.1 Subject Inclusion Criteria
All criteria below must be met for a Subject to be eligible for study participation.

- -Women at least 18 years of age and before the menopause (absence of menstruation for 12 months)
- -Experience moderate to severe pain (minimum of 5/10 on a numerical rating scale in at least 90 % of attempted sexual intercourse)

-Pain limited to the vestibule during vaginal intercourse and during activities exerting pressure on the vestibule (tampon insertion, tight jeans or pants, cycling, horseback riding)

- Presence of VBD for at least 6 months and diagnosed according to the standardized gynecological examination protocol by one of our staff gynecologists

- Have a stable sexual partner (sexual activity should include some attempted vaginal penetrations to evaluate pain intensity)

-Subject is willing to attempt sexual activity between visits

- Read and signed informed consent.

4.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria shall be excluded:

-Active vulvo-vaginal infections at the time of their gynecological examination.

-Genital bleeding of unknown origin

-Patients concomitantly included in different interventional clinical trials.

-Unwillingness to provide the informed consent to the trial.

- Women who were used topical drugs in the past 30 days

-Women with concomitant vulvar dermatosis or other vulvar disorders

4.3 Subject Withdrawal Criteria

The Principal Investigator may discontinue a subject's participation in the study at any time if it is considered in the subject's best interest to do so. Such a decision may be precipitated by adverse events, new onset illness, clinically important changes in vital signs, physical examinations, or laboratory tests. Subjects who are noncompliant with study procedures and visits may also be withdrawn by the Principal Investigator. Subjects may withdraw from participation in the study at any time for any reason. A subject's decision to withdraw will not cause the subject to lose any benefits to which she is entitled. A subject who withdraws prematurely from the study will return to the clinic as soon as possible to undergo the final visit evaluations.

If a subject prematurely withdraws or is withdrawn from study participation, the reason for the withdrawal must be recorded on the case report form (CRF).

Record the primary reason for premature withdrawal according to the following categories:

• Adverse Event: Subject experiences an intolerable event, which may or may not be related to the study medication.

• Withdrawn Consent: Subject withdraws from study participation for personal reasons (exclude adverse experience before indicating this category).

• Concomitant Medication Violation: Subject initiates, discontinues, or changes dosing regimen of concomitant medication in violation of the protocol, which, in the judgment of the Principal Investigator, may adversely affect evaluation of safety.

• Lost-to-Follow-up: Subject does not return for evaluation and no further contact is made by the Subject after three documented phone or email attempts and a final attempt by certified mail.

• Other: Any reason that does not fit in the above 4 categories: the reason will also be recorded on the CRF.

5. OUTCOMES

Primary efficacy outcome includes changes of symptoms evaluated through:

- 0-10 point visual scale (VAS) related to vulvar burning/pain and dyspareunia
- Vestibular cotton swab test (small cotton-tipped applicator lightly rolled over the surfaces of the vestibule (mean of values at the 1, 3, 5, 6, 7, 9, and 11 o'clock locations by asking the subject to report pain intensity on a discrete visual analog scale of 1 (no pain) to 10 (worst possible pain).
- Changes on validated instrument Vulvar Pain Functional Questionnaire (V-Q)

6. Clinical Procedures

Clinical procedures throughout the study are described in the sections below.

6.1 Informed Consent

Each potential study Subject must provide written informed consent and authorize release of her protected health information before any study procedure is conducted.

6.2 Study Day 0 . Subjects Screening and Visit 1

Candidates for enrollment will be screened within 15 days prior to enrollment. Before initiation of any test procedures, Subjects will be fully informed of the study plan, procedures, and risks involved in participating in the study. Each potential Subject will be required to read and to indicate her understanding by signing and dating the ICF prior to initiation of any screening procedures.
Screening procedures will consist of the following:

- Physical examination and medical history will be collected
- Evaluation of symptoms: 0-10 point visual scale (VAS) related to dyspareunia and vulvo-vaginal pain/burning
- Completion of validated questionnaire V-Q
- Vulvoscopy with evaluation of vestibular cotton swab test
- Evaluation of hypertonic pelvic floor established by a physical exam documenting hypertonus of the levator ani using an empirical score that allows reproduction of pelvic floor hypertonus with acceptable reliability (grade 0= no hypertonicity; grade 1= mild hypertonicity; grade 2= moderate hypertonicity and grade 3= severe hypertonicity

Subject meeting inclusion and exclusion criteria will be enrolled and will receive a dispenser system contains gel of CBD 5% *plus* myrcene or placebo (only vehicle without the actives). One or more members of the staff who do not work directly with the subject will be responsible for assignment to active or placebo treatment based on random assignment. The patients will be trained to apply the gel to the vulvar vestibule (2 puff of the dispenser) once a day for 60 days, before the bedtime.

6.3 Study Day 60± 3 days:

Patient who completed the treatment, will receive:

-Evaluation of symptoms: 0-10 point visual scale (VAS) related to dyspareunia and vulvo-vaginal pain/burning
- Completion of validated questionnaire V-Q
- Vulvoscopy with evaluation of vestibular cotton swab test
- Evaluation of pelvic floor hypertonicity
-Assessment of side effects

7. Statistical Methods

7.1 Determination of Sample Size

We used http://statulator.com program which calculated sample size for paired differences. With power of 80% and level of significant of 5%, for detecting a mean of the differences of VAS scale of 1.5 (20%) between pairs, assuming the standard deviation of the differences to be 2 we will need to recruit 40 participants, 20 for each group.