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Transmucosal delivery of cannabidiol using vestibular electroporation in patients with vestibulodynia: a randomized, blinded prospective trial

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Study Typology : randomized, blinded 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. The recommendations are in favor of a multi-dimensional approach, focusing on the management of pain and restoration of proper pelvic floor function.

References

-Pukall CF, Goldstein AT, Bergeron S, Foster D, Stein A, Kellogg-Spadt S, Bachmann G. Vulvodynia: Definition, prevalence, impact, and pathophysiological factors. J Sex Med 2016 Mar 1;13(3):291-304.
-Wesselmann U, Bonham A, Foster D. Vulvodynia: Current state of the biological science. Pain 2014 Sep;155(9):1696.

2. STUDY OBJECTIVE

The Research Hypothesis for the present study is to prospectively document the efficacy and safety of transmucosal delivery of cannabidiol using vestibular electroporation 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. Electroporation (EP) is the transitory structural perturbation of lipid bilayer membranes due to the application of high voltage pulses. Its topical application has been shown to increase the transdermal delivery of drugs with different order of magnitude. The presumption is to reach the area of clinical interest with a higher concentration of active ingredient achieving high efficacy and minimal side effects.

References

-Vuckovi ˇ c S, Srebro D, Vujovi ´ c KS, ´Vuceti ˇ c´ C and Prostran M (2018) ˇ Cannabinoids and Pain: New InsightsFrom

-Murina F - Transmucosal delivery of macromolecules using vaginal electroporation to treat vestibulodynia: A pilot study- Clin Obstet Gynecol Reprod Med, 2017 doi: 10.15761/COGRM.1000196

3. 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 instruments: Female Sexual Function Index (FSFI), Vulvar Pain Functional Questionnaire (V-Q)

Secondary objectives include evaluation of current perception threshold (CPT) testing, a technique which quantifies the sensitivity of vestibular nerve fibers and vaginal EMG measurements, collected at states of rest and during several exercises of the pelvic floor through an EMG device with a vaginal sensor (Myotonus plus©-London-UK)

The CPT values will be measured using the Neurometer CPT/C electrodiagnostic neurostimulator (Neurotron, Inc., Baltimore, MD), which emits constant alternating sinusoid waveform current stimuli at frequencies of 2000 Hz (specific for large, myelinated Ab fibers), 250 Hz (specific for Ad fibers), and 5Hz (specific for C fibers), at intensity levels from 0.001 to 9.99mA. Vulvar vestibule CPT values (1=0.01 mA) will be determined using a G-trode Vaginal/ Rectal Electrode (Neurotron, Inc., Baltimore, MD).

4. DESCRIPTION OF RESEARCH DESIGN

4.1 Overall Study Plan

This is an interventional, randomized and blinded prospective trial on one cohort of patients to be conducted at Lower Genital Tract Unit-Obst. and Gyn, Dept. –V. Buzzi Hospital-University of Milan-Milan, Italy. Subject's meeting inclusion and exclusion criteria will receive one treatment cycle of transmucosal delivery of cannabidiol using vestibular electroporation consists of 6 treatments, once a week. This is followed by follow-up visits at 4 and 8 weeks.

4.2 Study Duration

Each eligible subject will participate in the study for approximately 3-6 months depending upon which arm is assigned at randomization. It is expected this investigator-initiated research study will be completed approximately 6 months following initial approval by the Institutional Ethical Board.

4.3 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.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

The study population will include women with VBD.

5.1 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.

5.2 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.

5.3 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.

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 up to -30 days. Subject 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 questionnaires FSFI and V-Q
- Vulvoscopy with evaluation of vestibular cotton swab test
- Assessment of vestibular CPT evaluation using the Neurometer CPT/C, electrodiagnostic neurostimulator (Neurotron, Inc., Baltimore, MD)
- Assessment of vaginal EMG measurements, collected at states of rest and during several exercises of the pelvic floor through an EMG device with a vaginal sensor (Myotonus plus©-London-UK)

6.3 Study Day 0 days: Treatment 1

Subject meeting inclusion and exclusion criteria will be enrolled and first transmucosal delivery of 3ml CBD 8% gel (active group) or 3ml gel (placebo group) using vestibular electroporation (Vagy Combi- Top Quality Health) treatment will be performed. Vagy Combi is a device that combines radiofrequency with electroporation to enhance the active substance penetration.

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 gel for electroporation containing equal parts of CBD and placebo (gel without CBD) were placed in plastic bags and randomly distributed to operator who will perform the treatment.

6.4 Study Day 7 ± 1 days: Treatment 2

-Assess adverse events
- Treat vulvar vestibule region with CBD or gel through electroporation

6.4 Study Day 14 ± 1 days: Treatment 3

-Assess adverse events
- Treat vulvar vestibule region with CBD or gel through electroporation

6.5 Study Day 21 ± 1 days: Treatment 4

-Assess adverse events
- Treat vulvar vestibule region with CBD or gel through electroporation

6.6 Study Day 28 ± 1 days: Treatment 5

-Assess adverse events
- Treat vulvar vestibule region with CBD or gel through electroporation

6. 7 Study Day 35 ± 1 days: Treatment 6

-Assess adverse events
- Treat vulvar vestibule region with CBD or gel through electroporation
-Evaluation of symptoms: 0-10 point visual scale (VAS) related to dyspareunia and vulvo-vaginal pain/burning and vestibular cotton swab test

6.8 Study Day 65 ± 4 days: Follow-Up 1 (Visit 2) or Crossover Visit

Subjects assigned to active group:

-Evaluation of symptoms: 0-10 point visual scale (VAS) related to dyspareunia and vulvo-vaginal pain/burning
- Completion of validated questionnaires FSFI and V-Q
- Vulvoscopy with evaluation of vestibular cotton swab test
-Assessment of vestibular CPT evaluation using the Neurometer CPT/C, electrodiagnostic neurostimulator (Neurotron, Inc., Baltimore, MD)
-Assessment of vaginal EMG measurements, collected at states of rest and during several exercises of the pelvic floor through an EMG device with a vaginal sensor
-Assess adverse events

Subjects assigned to placebo group crossover complete visit 2 procedures today and follow protocol through to Visit 2 with active treatment.

6.9 Study Day 95 ± 4 days: Follow-Up 2 (Visit 3)

-Evaluation of symptoms: 0-10 point visual scale (VAS) related to dyspareunia and vulvo-vaginal pain/burning
- Completion of validated questionnaires FSFI and V-Q
- Vulvoscopy with evaluation of vestibular cotton swab test
-Assessment of vestibular CPT evaluation using the Neurometer CPT/C, electrodiagnostic neurostimulator (Neurotron, Inc., Baltimore, MD)
-Assessment of vaginal EMG measurements, collected at states of rest and during several exercises of the pelvic floor through an EMG device with a vaginal sensor
-Assess adverse events

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 60 participants, 30 for each group.

Appendice 1.

Sintesi del programma e delle procedure dello studio

Giorni dello studio	**Fino a -15**	**0**	**7± 1**	**14± 1**	**21± 1**	**28± 1**	**35± 1**	**65± 4***	**95± 4**
Visita o trattamento (T)	**1**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**2-FU1**	**3-FU2**
Consenso Informato	X								
Criteri Incl./Escl.	X	X							
Anamnesi	X								
Es.Obiettivo	X								
EMG muscoli pelvici e valutazione CPT vestibolare	X							X	X
Questionari validati	X							X	X
VAS bruciore /dolore e dispareunia	X						X	X	X
Vulvoscopia	X						X	X	
Cotton Swab test	X						X	X	
Elettroporazione con CBD o placebo		X	X	X	X	X	X		
Registraz. eventi avversi		X	X	X	X	X	X	X	X

* Per le pazienti del gruppo placebo seguire lo schema sottostante; FU=Follow-up

Giorni dello studio	**65± 4**	**72±1**	**79± 1**	**86± 1**	**93± 1**	**100± 1**	**130± 4**	**160± 4**
Visita o trattamento (T)	**FU1-T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**4-FU1**	**5-FU2**
Consenso Informato								
Criteri Incl./Escl.								
Anamnesi								
Es.Obiettivo								
EMG muscoli pelvici e valutazione CPT vestibolare	X						X	X
Questionari validati	X						X	X
VAS bruciore /dolore e dispareunia	X					X	X	X
Vulvoscopia	X					X	X	X
Cotton Swab test	X					X	X	X
Elettroporazione con CBD o placebo	X	X	X	X	X	X		
Registraz. eventi avversi	X	X	X	X	X	X	X	X