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Title of protocol

Treatment of Pelvic Floor Hypertonic Disorders with top Flat Magnetic Stimulation in Women with Vestibulodynia: a multicentric, randomized, blinded prospective trial.

Principal Investigator: Prof. Filippo Murina

Sites of research:
-Lower Genital Tract Unit-Obst. and Gyn, Dept. –V. Buzzi Hospital-University of the Study of Milan-Milan, Italy (Prof. Filippo Murina)
-Department of Obstetrics and Gynecology, Hospital State of Republic of San Marino, Borgo Maggiore, San Marino. (Dr. Maurizio Filippini)
-Pelvic Floor Unit, S.Gerardo Hospital-Monza-Italy. (Dr. Matteo Frigerio)

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. 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. 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. The recommended first-line treatment for high-tone pelvic floor dysfunction is pelvic floor physical therapy and rehabilitation.

2. TRIAL OBJECTIVE

The Research Hypothesis for the present study is to prospectively document the efficacy and safety of a new device that uses Top Flat Magnetic Stimulation for vulvodynia management (DR ARNOLD's chair). In recent years, magnetic stimulation has been investigated as a treatment for clinical neurodiagnostic applications and urological diseases as a safe and noninvasive method for nerve and muscle tissue stimulation. A pilot study demonstrated good improvement of symptoms related to VBD using Dr. ARNOLD device. Dr. ARNOLD (DEKA M.E.L.A. Calenzano, Italy) is a noninvasive therapeutic system that selectively stimulates the female pelvic floor muscles through programmed specific contractions and relaxations to improve pelvic floor dysfunctions. The stimulation is generated by electromagnetic fields with a homogenous profile (TOP FMS–TOP Flat Magnetic Stimulation) optimized for stimulation of the pelvic area. The interaction with the tissue includes muscular contraction, depolarization of neuronal cells, and influence on the blood circulatory system. The presumption is to reach the area of clinical interest with a higher precision achieving high efficacy and minimal side effects.

3. OUTCOMES

Primary efficacy outcome includes changes of symptoms and signs 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).
- Clinical evaluation of hypertonus of the levator ani complex by an experienced examiner using an empirical score:
  - grade 0= no hypertonicity
  - grade 1= mild hypertonicity
  - grade 2= moderate hypertonicity
  - grade 3= severe hypertonicity

Secondary objectives include evaluation of vaginal EMG measurements. Vaginal EMG measurements will take at states of rest and during several exercises of the pelvic floor through an EMG device with a vaginal sensor. PFM activity at rest was measured as the mean muscle tone value at rest after six maximum contractions separated by a rest period of at least 12 s, while the PFM peak activity was calculated as the mean of six maximum voluntary contractions separated by a rest period of at least 12s. The

assessments also included the PFM strength that was obtained by subtracting the maximal value from resting values.

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 three different sites:

- -Lower Genital Tract Unit-Obst. and Gyn, Dept. –V. Buzzi Hospital-University of Milan-Milan, Italy.
- - Department of Obstetrics and Gynecology, Hospital State of Republic of San Marino, Borgo Maggiore, San Marino.
- - Pelvic Floor Unit, S.Gerardo Hospital-Monza-Italy

Subject's meeting inclusion and exclusion criteria will receive one cycle of 6 treatments, once a week. This is followed by follow-up visits after 4 weeks.

4.2 Study Duration

Each eligible subject will participate in the study for approximately 2-4 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.

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) consistent with the VBD diagnosis.
- Presence of VBD for at least 6 months and diagnosed according to the standardized gynecological examination protocol by one of our staff gynecologists
-Subject is willing to attempt sexual activity between visits (sexual activity should include some attempted vaginal penetrations to evaluate pain intensity)
-Read and signed informed consent.
-They had been diagnosed with moderate or severe pelvic floor hypertonic dysfunction
-They did not receive a pelvic floor rehabilitation in the past 2 months

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.
-Were in pregnancy
-Persons with pacemakers or metal implants
-Unwillingness to provide the informed consent to the trial.

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. Clinical Procedures

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

5.1 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.

5.2 Subject Screening and Visit 1 (Treatment 1)

Candidates for enrollment will be screened within 10 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
- Clinical evaluation of hypertonus of the levator ani complex
- Evaluation of vestibular cotton swab test
- 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

-Subject meeting inclusion and exclusion criteria will be enrolled and first Dr. ARNOLD session with active or sham treatment will be performed. One or more members of the staff who do not work directly with the subject will be responsible for assignment to active or sham treatment based on random assignment.

5.3 Study Day 7 ± 1 days: Treatment 2

-Assess adverse events

- Treatment with DR. ARNOLD device

5.4 Study Day 14 ± 1 days: Treatment 3

-Assess adverse events

- Treatment with DR. ARNOLD device

5.5 Study Day 21 ± 1 days: Treatment 4

-Assess adverse events

-Treatment with DR. ARNOLD device

5.6 Study Day 28 ± 1 days: Treatment 5

-Assess adverse events

- Treatment with DR. ARNOLD device

5. 7 Study Day 35 ± 1 days: Treatment 6

-Assess adverse events

- Treatment with DR. ARNOLD device

5.8 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

- Vulvoscopy with evaluation of vestibular cotton swab test

-Clinical evaluation of hypertonus of the levator ani complex

-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 sham group complete visit 2 procedures today and follow protocol through to Visit 2 with active treatment.

6. Statistical Methods

6.1 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.

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