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Title of protocol

Vaginal diazepam for the treatment of pelvic floor hypertonic dysfunction in patients with vestibulodynia: a double-blind, randomized, placebo-controlled trial

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Site of research: Lower Genital Tract Unit-Obst. and Gyn, Dept. –V. Buzzi Hospital-University of Milan-Milan, Italy

Synopsis

Title	Vaginal diazepam for the treatment of pelvic floor hypertonic dysfunction in patients with vestibulodynia: a double-blind, randomized, placebo-controlled trial
Type	Interventional, randomized, double-blind, placebo-controlled trial
Background	High-tone pelvic floor dysfunction, also known as hypertonic pelvic floor disorder, is a specific hypertonic condition in which the levator ani muscles spasm involuntarily or demonstrate a passive stiffness of the muscle, resulting in impaired reproducible pelvic floor pain, and sexual dysfunction. Recognition and clinical diagnosis of high-tone pelvic floor dysfunction is complicated by its overlap with several other clinical syndromes. Conditions such as vulvodynia, chronic pelvic pain and may often result in high pelvic floor tone. 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%). VBD is likely not one disease but rather several diseases, in which the common end point is vestibular hypersensitivity and pelvic floor hypertonic dysfunction. The recommended first-line treatment for high-tone pelvic floor dysfunction is pelvic floor physical therapy and rehabilitation. The use of intravaginal diazepam for treatment of high-tone pelvic floor dysfunction that is refractory to conservative therapy is becoming more common in clinical practice. However, there is a paucity of data regarding the efficacy, appropriate dosage, length of therapy, and risk of side effects with its off-label use for this indication.

Research Hypothesis	The Research Hypothesis for the present study is to assess the efficacy and safety of intravaginal diazepam for women with VBD.
Objectives	The primary objective is to evaluate the pelvic floor parameters changes and its correlations with patient's symptoms after using of intravaginal diazepam for 45 days
Outcomes	Objectives include evaluation and changes of: -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. physical exam documenting -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 - 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).
Design	Interventional, randomized, double-blind, placebo-controlled trial
Inclusion Criteria	- Diagnosis of VBD - Patients at least 18 years of age and before menopause -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 -Read and signed informed consent
Exclusion Criteria	-They had an allergy to diazepam or any benzodiazepine -They are currently pregnant, -They had any contraindication to diazepam

	-Patients concomitantly included in different interventional clinical trials. -Unwillingness to provide the informed consent to the trial.
Number of patients and sample size	40 enrolled women (20 for group).
Statistical analysis	Quantitative variables (i.e. demographic) if normally distributed will be described through mean ± Standard Deviation (SD), otherwise median, minimum, maximum, and interquartile range will be showed. Qualitative variables will be evaluated using frequencies and percentages. In order to evaluate changes over time before and after the treatment, Paired t-test (if applicable) or Wilcoxon signed rank sum test will be performed for quantitative variables, while McNemar test will be used in order to evaluate changes for binary variables, while symmetry test will be performed in order to evaluate changes for qualitative (not binary) variables. The quality and completeness of the collected data will be evaluated preliminarily compared to data analysis. If a subject is missing information for one or more variables, even after the resolution of its query, the missing data will not be replaced. If a subject has been involved in violation of inclusion/exclusion criteria, the respective data will be excluded from the analysis.
Protocol	The original intent-to treat includes 40 women randomized to receive one of the two treatment groups as follows: -Group 1: vaginal suppositories containing diazepam 5mg, daily for four weeks -Group 2: vaginal suppositories containing only excipients, daily for four weeks
Procedures	a) Screening and Baseline Visit (day 1). Before initiation of any test procedures, Subjects will be fully informed of the study plan, procedures, and risks involved in participating in the study. - 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 -Vulvoscopy with evaluation of vestibular cotton swab test - Clinical evaluation of hypertonus of the levator ani complex by an experienced examiner using an empirical score - 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 will be randomly and blindly assigned to one of two groups to receive diazepam or placebo vaginal suppositories. Identical vaginal suppositories containing 5 mg of diazepam or placebo will be received from the manufacturer in separated boxes with the same color and they were numbered randomly by staff not participating in the study. Investigators were blinded to the randomization code until all data were analyzed. Treatment instructions will be to insert one vaginal tablet daily before going to sleep for 45 days, except during the menstrual phase. Before randomization, patients were asked to stop any topical or systemic therapy

	b) Final visit of follow up (day 60). Subject will report to the Principal Investigator's office for the following procedures: -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 - Clinical evaluation of hypertonus of the levator ani complex by an experienced examiner using an empirical score -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