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Vaginal diazepam plus transcutaneous electrical nerve stimulation to treat vestibulodynia: A randomized controlled trial

Filippo Murina*, Raffaele Felice, Stefania Di Francesco, Silvia Oneda

Lower Genital Tract Disease Unit, V. Buzzi Hospital–University of Milan, Milan, Italy

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ABSTRACT

Objective: To assess the effectiveness of vaginal diazepam in addition to transcutaneous electrical nerve stimulation (TENS) in the treatment of vestibulodynia (VBD).
Study Design: This study was a randomized, double-blind, placebo-controlled trial. Forty-two patients with VBD were randomized, 21 underwent diazepam and TENS (diazepam group) and 21 received placebo and TENS (placebo group). Vulvar pain was assessed on a on a 10-cm visual analogue scale (VAS) and dyspareunia according to the Marinoff dyspareunia scale. Vaginal surface electromyography (EMG) and vestibular current perception threshold (CPT) testing were performed at baseline and 60 days after treatment. The primary endpoints included the change in pain and dyspareunia from baseline to 60 days of pain and dyspareunia. The secondary endpoints was the variation in objectivity of pelvic floor muscle (PFM) function and vestibular nerve fiber current perception threshold (CPT).
Results: The VAS scores for pain from basal values of 7.5 and 7.2 for the diazepam and placebo, respectively, showed significant (p 0.01) decreases from 4.7 to 4.3, but this difference was not statistically significant. The Marinoff dyspareunia scores in the diazepam group showed a significant difference (p 0.05) from values measured in the placebo group. The ability to relax the PFM after contraction (difference between maximal contraction and rest tone) was significantly greater for the diazepam group versus the placebo group (3.8 μv and 2.4 μv, respectively, p 0.01). The CPT values for all of the nerve fibers increased after the treatment, but this increase was significant in the diazepam group only for the values at a 5-Hz stimulation (C fibers) with a change of 47.8% vs 26.9% ($p < 0.05$). Only two patients reported a mild drowsiness in the diazepam group.
Conclusions: The present study provided indications that vaginal diazepam plus TENS is useful to improve pain and PFM instability in women with VBD.

Introduction

Vulvodynia is a prevalent form of chronic vulvar pain, affecting as many as 17% of women within their lifetime [1,2]. Localised provoked vulvodynia at the vestibule, known as VBD, is the most common manifestation of the disease [3]. Vulvodynia includes patients experiencing vulvar pain or discomfort for a duration of at least three months, and it seems to have no clear identifiable causes but may have potential associated factors (e.g., genetic and/or immune factors, hormonal factors, inflammation and neuropathic changes) [4,5]. However, given the variable presentations and individualized responses to treatment, vulvodynia causation is most likely multifactorial, where the associated factors are themselves pathophysiological components of the disease with a different relevance in each individual. PFM dysfunctions are present in a significant proportion of women with VBD. High resting tension, muscle irritability, tenderness to palpation, and overall weakness seems of greatest importance in the pathophysiology of genital pain [6].

Although the optimal treatment remains unclear, an individualized, multimodal approach should be considered to address all aspects of VBD pain. Such modalities as vaginal and external soft tissue mobilization and myofascial release, and biofeedback with surface EMG, have been used to correct PFM dysfunction in VBD patients [7,8]. TENS, a physical therapy modality, was demonstrated to be effective in patients with VBD [9,10]. Due to its use in the treatment of muscle spasms, the effect of vaginal diazepam on pelvic floor dysfunction and vulvar pain has been evaluated [11,12]. We conducted a double-blind placebo-controlled study to investigate the effectiveness of vaginal diazepam in addition to TENS on the treatment of VBD. We suggest that the synergy of the effect of the two therapies as a multimodal treatment strategy could improve both vulvar pain and PFM dysfunctions.

* Corresponding author at: Via Castelevetro 24-Milan, Italy.
E-mail address: filippomurina@tin.it (F. Murina).

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Materials and methods

The study was designed as a randomized, double-blind, placebo-controlled trial. Institutional Review Board approval for the study was obtained, and it was registered at http://www.isrctn.com (ISRCTN12345678). Subjects were eligible for enrollment if they had a diagnosis of VBD, were at least 18 years of age, and if they had been diagnosed with moderate or severe pelvic floor hypertonic dysfunction. The diagnosis of hypertonic pelvic floor needed to be established by a physical exam documenting hypertonus of the levator ani complex by an experienced examiner (FM, RF). We used 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) [13]. Subjects were excluded if they had an allergy to diazepam or any benzodiazepine, were currently pregnant, or had any contraindication to diazepam. Women with VBD filled in questionnaires and underwent a gynecological examination, including vulvo/colposcopy. The International Society for the Study of Vulvovaginal Disease vulvodynia questionnaire [14] was used in this study. Women found suitable for the study underwent a vulvar cotton swab examination (at the 1, 3, 5, 7, 9, and 11 o'clock positions around the vaginal opening at Hart's line) to confirm the diagnosis of VBD and the sensitivity around the vestibule was scored. At the first assessment, symptoms of burning and pain were evaluated on a 10-cm VAS. Dyspareunia was recorded and graded on a 0–3 score according to the Marinoff dyspareunia scale [15]. Grade 1 is characterized by intercourse that is always painful but only occasionally prevents penetration, grade 2 is characterized by intercourse that is always painful and often prevents penetration, and grade 3 is characterized by complete apareunia.

Following consent to participate, all subjects underwent vaginal surface EMG. Vaginal EMG measurements were taken at states of rest and during several exercises of the pelvic floor through an EMG device with a vaginal sensor (Myotonus plus©-London-UK). 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 12 s. The assessments also included the PFM strength that was obtained by subtracting the maximal value from resting values [16]. In addition to EMG measures, the CPT testing, which quantifies the functional integrity of specific afferent nerve fibers from the periphery to the central nervous system, was collected. The CPT values were measured using the neurometer CPT/C electrodiagnostic neurostimulator (Neurotron, Inc., Baltimore, MD), which emits sinusoid waveform constant alternating current stimuli at frequencies of 2000 Hz (specific for large, myelinated Aβ fibers), 250 Hz (specific for Aδ fibers) and 5 Hz (specific for C fibers), at intensity levels from 0.001 to 9.99 mA [17].

Vulvar vestibule CPT values (1 = 0.01 mA) were determined using a G-trode Vaginal/Rectal Electrode (Neurotron Inc, Baltimore, MD). At each frequency, stimulus intensity was incremented from 0 to a maximum of 9.99 mA until the patient was able to detect a sensation around the site of the electrode and was represented at decreasing intensities until it was no longer detected within a range of 0.10 mA. The patient was then presented with a series of choice tests consisting of randomly generated pairs of real and false (placebo) stimuli along with pairs of false stimuli, with each stimulus separated by a rest period. The threshold was determined after a minimum of seven consecutive consistent forced-choice presentation responses. Patients were randomly and blindly assigned to one of two groups to receive diazepam or placebo vaginal tablets. Identical vaginal tablets containing 5 mg of diazepam or placebo were 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. The vaginal tablet containing equal parts of diazepam and placebo (cornstarch) were placed in plastic bags and randomly distributed to patients enrolled in the study. Before randomization, patients were asked to stop any topical or systemic therapy they were taking until at least 30 days before starting therapy. Treatment instructions were to insert one vaginal tablet daily before going to sleep for 60 days. All patients received TENS therapy in a self-administered domiciliary protocol. A dual channel portable TENS unit (NeuroTrac Continence; VerityMedical, London, UK) was used.

The stimulation was delivered through a commercially available plastic vaginal probe (Periprobe VAG2ST Beac, Pavia, Italy) that was 20 mm in diameter and 110 mm in length with two gold metallic transversal rings as electrodes. It was inserted into the vagina for 20 mm.

Two customized programs were set according to our previous studies [9,10]. The standard protocol for TENS was 15 min of 100-Hz frequency and a pulse duration of 50 μs (first program) followed by 15 min of 5-Hz frequency and a pulse duration of 100 μs (second program). All patients received a supervised trial consisted of 6–7 sessions and served to familiarize the patient on the use of TENS, while allowing the therapist to check that the patient was using the device properly. In the TENS treatment protocol, the pulse was increased rapidly until the patient reported the onset of any sensation under the electrodes. The intensity was then increased slowly until this sensation reached a level described as the maximum tolerable without experiencing pain. After completing the trial, the patient was consigned their TENS unit after verbal and written instructions, with a recommendation to perform home treatment 3 times each week.

The primary efficacy endpoint for this study included the mean change from baseline to 60 days of pain and dyspareunia. The secondary endpoint was the variations in objectivity (PFM parameters and vestibular nerve fibers CPT).

Assuming an anticipated cure rate of 70% in the control group arm, a minimum of 20 subjects per group was required to detect an increase in the cure rate compared with 80% in the group supplemented with vaginal diazepam, assessed at the 2-sided 5% level of significance with 80% power. All statistical analyses were performed using SPSS, Version 20.0 (IBM Corp., Armonk, NY). Rates and proportions were calculated for categorical data and medians and ranges for continuous data. Differences in continuous variables were analyzed by means of a Student's *t*-test (normally distributed values) or Mann–Whitney U test (non-normally distributed data). For categorical variables, differences were analyzed by the mean of a chi-square test.

All reported p values are two sided and a p value of <0.05 was considered to indicate statistical significance.

Results

Of 65 women meeting the inclusion criteria of the study, 42 agreed to participate in the study and 21 were randomized to diazepam + TENS (diazepam group) and 21 to placebo + TENS (placebo group). No patients were lost to follow-up, thus all the 42 subjects completed the study (Fig. 1). No significant difference between groups was found in the demographic data before treatment (Table 1). The mean value of the PFM hypertonus palpation scores before the therapy was 2.5 (SD 1.4) for the total sample, without any significant differences between the two study groups. The mean value was 2.6 (SD 1.5) for the diazepam group and 2.3 (SD 0.5) for the placebo group, p 0.2 (Table 1). The distribution of symptoms and vaginal EMG measurements at