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Title of protocol

A blind controlled prospective study to compare two TENS transvaginal programs setting with different parameters in patients with vestibulodynia

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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	A blind controlled prospective study to compare two TENS transvaginal programs setting with different parameters in patients with vestibulodynia
Type	Interventional, randomized clinical trial
Rationale and Research Hypothesis	Electrotherapy can treat diverse symptoms produced by diseases that affect the human body. Electrotherapy using Transcutaneous Electrical Nerve Stimulation (TENS) is a low-cost, non-invasive and easily accessible technique to treat pain . TENS acts by spinal blocking and endogenous opioids release Its parameters may be adjusted, widening its range of action on pain. Recent technological advances facilitated the use of self-applied TENS devices. It has been demonstrated that TENS is of significant benefit in the management of vestibulodynia, in fact it provides a therapeutic neuromodulation. Experimental investigations into the physiological effects of electrical stimulation suggest different analgesic responses with different parameter combinations. The stimulation parameters that are set on the TENS unit determine the type of nerve fibers stimulated and thus its mechanism of action.
	The Research Hypothesis for the present study is to compare the effects of different Tens parameters in the treatment of patients with vestibulodynia

Objectives	-The primary objective is to compare the effects of two TENS transvaginal programs setting with different parameters in patients with vestibulodynia -The secondary objective of the trial is to rate the relationship between effectiveness and numbers of TENS session over time.
Outcomes	Primary outcomes: evaluation of symptoms related to VBD through: -0-10 point visual scale (VAS) related to: - dyspareunia and vulvo-vaginal pain/burning - vestibular cotton swab test (small cotton-tipped applicator lightly rolled over the surfaces of the vestibule -Validated instruments including FSFI and Vulvar Pain Functional Questionnaire (V-Q) (Appendix 1) Secondary outcome: assessment of pelvic floor muscle (PFM) function by vaginal EMG measurements 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) (Appendix 2)
Design	Interventional, double-blind controlled prospective trial on one cohort of patients.
Inclusion Criteria	- Were 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 provoked vestibulodynia (PVD) 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 in order to evaluate pain intensity)
Exclusion Criteria	• Women with pacemaker • Active vulvo-vaginal infections at the time of their gynecological examination. • Women currently pregnant • Genital bleeding of unknown origin • Patients concomitantly included in different interventional clinical trials. • Unwillingness to provide the informed consent to the trial.
Number of patients and sample size	34 enrolled women (17 for group). Assuming an anticipated cure rate of 70% in the control group arm, a minimum of 17 subjects per group was required to detect an increase in the cure rate compared with 80% in the group with different TENS parameters, assessed at the 2-sided 5% level of significance with 80% power.

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 34 women randomized to receive: <u>Group 1</u> – Two vaginal TENS programs setting with parameters used in previous study with TENS in vestibulodynia <u>Group 2</u> – Two vaginal TENS programs setting with parameters used in recent experimental studies of TES in neuropathic pain All patients will receive TENS therapy in a self-administered domiciliary protocol through a portable TENS unit (EVA-Sirval-Italy), which produces a symmetrical biphasic wave and has customizable mode programs. The stimulation will be delivered through a plastic vaginal probe that is 20 mm in diameter and 110 mm in length with two gold metallic transversal rings as electrodes. It will be inserted into the vagina for 20 mm. After completing two trial sessions with the operator, the patient will be given their TENS unit after verbal and written instructions, with a recommendation to perform home treatment 3 times each week
Procedures	<u>a) Screening and Baseline Visit (Visit 0)</u> - 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 pelvic floor muscle (PFM) function by vaginal EMG measurements -Scheduling two trial sessions with subsequent delivery of TENS unit <u>b) Visit 1 (day 60±3 after the start of TENS).</u> - 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

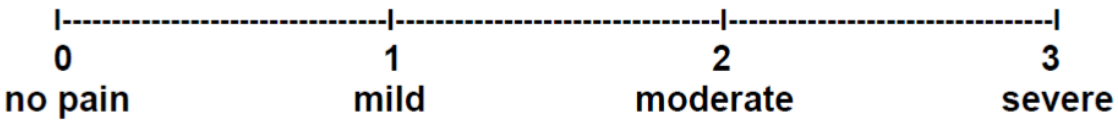
	- assessment of pelvic floor muscle (PFM) function by vaginal EMG measurements -assessment of adverse effects c) Visit 2 (day 120±3 after the start of TENS). - evaluation of symptoms: 0-10 point visual scale (VAS) related to dyspareunia and vulvo-vaginal pain/burning - completion of validated questionnaires FSFI and V-Q - vulvoscopy with evaluation of vestibular cotton swab test - assessment of pelvic floor muscle (PFM) function by vaginal EMG measurements -assessment of adverse effects

-Appendix 1: see enclosed paper for validated questionnaires FSFI and V-Q

-Appendix 2: assessment of pelvic floor muscle (PFM) function by vaginal EMG measurements

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 seconds, while the PFM peak activity was calculated as the mean of six maximum voluntary contractions separated by a rest period of at least 12 seconds. The assessments also included the PFM strength that was obtained by subtracting the maximal value from resting values

Appendix 1: pain scale for vestibular and vaginal swab test



Appendix 2: vestibular and vaginal trophism

-Vestibular trophism

-Vaginal trophism (VHI)

Observation	0 - none	1 - mild	2 - moderate	3 - severe
Petechiae				
Pallor				
Friability				
Dryness				
Redness				

Table 3
Vaginal health index

Overall elasticity[a]	Fluid secretion type and consistency	pH	Epithelial mucosa	Moisture
1 None	None	6.1	Petechiae noted before contact	None, Mucosa inflamed
2 Poor	Scant, thin yellow	5.6–6.0	Bleeds with light contact	None, mucosa not inflamed
3 Fair	Superficial, thin white	5.1–5.5	Bleeds with scraping	Minimal
4 Good	Moderate, thin white	4.7–5.0	Not friable, thin mucosa	Moderate
5 Excellent	Normal (white flocculent)	≤ 4.6	Not friable, normal mucosa	Normal

[a]Lower score corresponds to greater urogenital atrophy.