

Research Article

Transmucosal delivery of macromolecules using vaginal electroporation to treat vestibulodynia: A pilot study

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Abstract

Background: Provoked vestibulodynia (VBD), is characterized by burning and cutting pain localized to the vulvar vestibule in response to light touch.

Objective: To assess the effectiveness of the electroporation (EP), applied through the vaginal probe using a mix of two drugs: amitriptyline + lidocaine in patients with a diagnosis of VBD.

Method: 17 patients with the diagnosis of VBD received a weekly vaginal EP for a total of eight sessions using the following mixture of drugs: amitriptyline at a dose of 60mg and lidocaine at a dose of 40 mg, all dissolved in a conductive gel. Visual analogue scale (VAS), Marinoff score for dyspareunia, and current perception threshold obtained from the vulvar vestibule were assessed at baseline and at the end of treatment.

Results: The VAS was reduced from a baseline of 7.4 (1.2) to a 6.3 post therapy (1.8), and despite the variation not apparently of large extent was actually statistically significant (p 0.05). Dyspareunia also reduced, from baseline of 2.3 (1.0) to a post- therapy of 1.8 (1.1) without statistical significance. There were no relevant side effects that prompted discontinuation of treatment.

Conclusions: Based on what aforementioned vaginal EP can be defined as an promising technique in the management of VBD. Although further studies are needed to define the number and frequency of sessions required, as well as the mix of drugs to be used.

Introduction

Vulvodynia is a common multifactorial, heterogeneous, and chronic gynecological disorder that affects a large number of women worldwide. It is estimated that the prevalence rate of vulvodynia is 16% in women aged 18 to 64 years, resulting in constant demand for medical care [1]. The predominant form of vulvodynia, provoked vestibulodynia (VBD), is characterized by burning and

cutting pain localized to the vulvar vestibule in response to light touch [2]. Etiology for vulvodynia has yet to be established, yet several theories exist. Numerous factors have been proposed and a relevant role appears to be that of a dysfunctional state of the somatosensory system, with a peripheral and central neural sensitization [2].

Vulvodynia may result from peripheral sensitization in the skin, central sensitization in the spinal cord, or both of them. An inflammatory process in the vulvar skin could release a cascade of cytokines that sensitize the nociceptors resulting in a physical increase in the number of nerves. Furthermore, the local sensory pain nerves could become progressively more sensitized, and develop abnormal neuro-secretion with ulterior pain deterioration or persistence [2-3]

There is no standard treatment of the disease, and few randomized controlled trials have been performed [4]. The recommendations are in favor of a multi-dimensional approach, focusing on the management of pain and restoration of proper pelvic floor function. Medical therapy (topical or oral) is a mainstay of the management of VBD [5]. Amitriptyline is a tricyclic antidepressant that effectively treats many conditions of chronic neuropathic pain [6]. It modulates the pain by acting on the central inhibition of neuronal reuptake of neurotransmitters and inhibition of sodium channels. Although oral administration of amitriptyline is the gold standard for the treatment

of neuropathic pain and it is often used in the VBD, the systemic side effects such as postural hypotension, sedation, anticholinergic effects limit the attainment of therapeutic doses.

The long-term use of topical lidocaine has been suggested as a specific therapy for VBD, with the rationale that the regular application of lidocaine interrupts the pain signals and reduces the pain amplification [7]. The use of local anesthetics in the long term can cause itching or sensitization, with severe reaction and contact dermatitis, especially with products such as benzocaine [8]. Transcutaneous electrical nerve stimulation (TENS) with biphasic currents of frequencies between 2 and 100 Hz and a pulse duration of 50-100 microsec, has been widely used with a high efficacy (75%) as compared to the placebo in the treatment of VBD [9].

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 [10]. In addition, the EP expands the range of drugs (macromolecules, lipophilic or hydrophilic, charged or neutral molecules) that can be delivered transdermally [11].

The aim of our study was to evaluate the effectiveness of the EP applied through the vaginal probe, using a mix of two drugs:

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amitriptyline + lidocaine in patients with a diagnosis of VBD. The presumption is to reach the area of clinical interest with a higher concentration of active ingredients, reaching higher concentration than systemic administration but with fewer side effects.

Material and methods

A total of 17 patients were enrolled. All had diagnosis of VBD due to the coexistence of the following conditions: a history of chronic vulvar pain elicited by stimulation or attempted intercourse and a positive cotton-swab test, that is tenderness at palpation of the vestibular area with a cotton tip applicator and the absence of any clinically detectable manifestation. Exclusion criteria were pregnancy, cardiac pacemakers, vaginal infections and neurological disorders.

The patients completed a questionnaire regarding their vulvovaginal situation, general health, demographic characteristics, and some questions about psychosexual factors.

Subsequently, each patient underwent a gynecological examination and evaluation of vulvovaginal symptoms with details concerning:

- Visual-analogue scale of pain (VAS) graduated from 0 to 10 (0 = no pain, 10 = maximum pain)

- Dyspareunia-graded by Marinoff score (0 = absent, 1 = mild, 2 = intense pain with reduced frequency of intercourse, 3 = penetration almost impossible).

Patients were also subjected to a sensory electrodiagnostic evaluation of the vestibular nerve conduction by measuring the minimum threshold of perception of a sensory input on the vestibular mucosa (CPT). The CPT values were measured using the Neurometer CPT/C electro diagnostic neurostimulator (Neurotron, Inc., Baltimore, MD), which emits alternating sinusoid waveform current stimuli at frequencies of 2,000 Hz (specific for large, myelinated AA fibers), 250 Hz (specific for AC fibers) and 5 Hz (specific for C fibers), at intensity levels from 0.001 to 9.99 mA.

Each woman included in the study received a weekly vaginal EP for a total of eight sessions through a plastic vaginal probe (Blumoon-Italy) with two transversal metal rings as electrodes connected to a unit calibrated for the EP (Blumoon-Italy).

The new probe has been designed with a slot for a 2.5 ml syringe, in which the product to be conveyed in the vestibular mucosa was placed. In the disposable syringe we inserted following mixture of drugs: amitriptyline at a dose of 60mg and lidocaine at a dose of 40 mg, all dissolved in a conductive gel. The EP unit was set with the following parameters of TENS, in agreement with previous studies that have used the technique in the treatment of VBD [9]:

- Phase I: 100 Hz - 50 ms- pulse duration for a duration of 15 min.
- Phase II: 5 Hz - 100 ms-pulse duration for a duration of 15 min.

The patients were re-evaluated at the end of treatment both from symptomatic point of view (VAS and Marinoff score of dyspareunia), and objectively through re-evaluation of the CPT.

Results

All the recruited patients completed the treatment protocol, and none were lost during follow-up. The characteristics of the patients studied are summarized in Table 1. The main age of the patients was 32,5 years (20-48 years). Eighty-eight percent of the patients were nulliparous (15/17). If we consider the mean duration of the symptoms was 27,5 months (6-80 months).

The VAS was reduced from a baseline of 7.4 (1.2) to a 6.3 post therapy (1.8), and despite the variation not apparently of large extent was actually statistically significant (p 0.05). Dyspareunia also reduced, from baseline of 2.3 (1.0) to a post- therapy of 1.8 (1.1) without statistical significance (Table 2).

Table 3 summarizes the values of the CPT baseline and post-therapy.

Most changes involved the subpopulation of nociceptive C fibers with 24.4 % reduction in sensitivity. In the group of Aβ and Aδ fibers, the reduction rate was respectively 15.5% and 20.4 %. There were no relevant side effects that prompted discontinuation of treatment, a post- treatment mild transient stinging was seen in about 7% of cases, and transient sedation in 10 % of patients.

Discussion

In VBD, unanimous pathophysiological data is the proliferation of nerve endings in the vestibular mucosa, which is considered a non-specific reaction of previous mucosal triggers, such as infection, trauma, and hormonal factors. Another factor observed in women with this disease is the dysfunction of the pelvic floor muscles, contracted around the distal part of the vagina, probably as a reaction to persistent pain. Amitriptyline is the most widely used oral medication, although its real usefulness in the treatment of VBD is not clear. The doses commonly used vary (30-100 mg) as can vary the percentage of the response, ranging between 30-60 % .This mainly derives from the difficulty in achieving an optimal therapeutic threshold resulting in high number of drop-outs due to the occurrence of side effects.

The lidocaine, a local anesthetic, has been used topically as well as in local infiltration of the pudendal nerve with the aim of reducing the ectopic neuronal activity, responsible for allodynia and hyperalgesia, peculiar elements of neuropathic pain syndromes as well as that of the VBD. A multimodal approach towards the VBD is considered to be optimal, and from this point of view association of TENS with the use of drugs may prove to be a winning strategy.

The EP allows to combine the electrical stimulation to the transmucosal transport of macromolecules even in high concentrations,

Table 1. Characteristics of the study population.

Age, mean (range) y	32.5 (20-48)
Nulliparous, n (%)	15/17 (88)
Duration of symptoms, mean (range), mo	27.5 (6-80)
VAS, mean (SD)	7.4 (1.2)
Marinoff dyspareunia scale, mean (SD)	2.3 (1.0)

VAS: Visual Analogue Scale

Table 2. Post treatment scores of VAS and Marinoff dyspareunia scale.

	n. 17 Patients	p
VAS, mean (SD)	6.3 (1.8)	0.05
Marinoff dyspareunia scale, mean (SD)	1.8 (1.1)	NS

VAS: Visual Analogue Scale

Table 3. Results of CPT measurement (100 = 1.0 mA) at 3 selected stimulation frequencies before and after therapy.

N. 17 patients	2,000 Hz (Aβ fibers)	250 Hz (Aδ fibers)	5 Hz (C fibers)
Basal	442,2	201,5	90,8
After therapy	523,4	253,3	120,2
Difference, %	15,5	20,4	24,4

Data are expressed as means (Hz = cycles per second). CPT: Current Perception Threshold

which are then focused at the site of pain elicitation, vaginal vestibule, thus reducing the incidence of side effects.

Our results suggest the effectiveness of the technique. The doses of amitriptyline and lidocaine that we used were high and no patient had to discontinue the treatment for the occurrence of side effects. The synergistic effect of TENS further contributed to the “reset” of the previously altered nociceptive system.

The demonstration of the absorption and action of drugs as a result of channeling through vaginal EP, is confirmed by CPT values. A 20 % average reduction of the sensitivity of vestibular nerve fibres proves the effect of the combination of TENS with that of drugs in the management of the dysfunction in the pain perception system, proper to the VBD.

A mild improvement of the symptoms may be due to the reduced frequency (1 appl./Week) and a relatively low number of EP vaginal sessions.

In fact, previous studies on TENS led to brilliant results with an average of approximately 20 sessions. Moreover, the patients recruited had already been treated with limited or transient efficacy, leading to define them as “difficult”.

Based on what aforementioned vaginal EP can be defined as an effective and promising technique in the management of VBD. Although further studies are needed to define the number and frequency of sessions required, as well as the mix of drugs to be used. It may further lead the foundation for the use of the technique in other vulvovaginal problems that require the use of drugs locally.

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