

The role of immunoenzymatic therapy in the management of vestibulodynia associated with painful bladder syndrome

Filippo Murina, Raffaele Felice, Stefania Di Francesco, Valeria Mantegazza

Outpatient Department of Vulvar Disease, V. Buzzi Hospital-University of Milan, Milan, Italy
Email: filippomurina@tin.it

Received 18 March 2013; revised 20 April 2013; accepted 28 April 2013

Copyright © 2013 Filippo Murina *et al.* This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Vestibulodynia (VBD) and painful bladder syndrome (PBS) are two common and often concomitant conditions. **Objective:** To assess the effectiveness of an enzymatic combination of papain, bromelain, trypsin, chymotrypsin and quercetin in the supportive treatment of VBD/PBS, patients underwent TENS + amitriptyline and pregabalin therapy as a multimodal treatment strategy. **Method:** 40 patients were randomly assigned to receive a systemic therapy: amitriptyline + pregabalin (Group A) versus amitriptyline + Pregabalin plus a systemic enzyme preparation (Group B). All patients received a transcutaneous electric nerve stimulation (TENS) therapy in a self-administered domiciliary protocol. **Results:** The VAS and the dyspareunia score after the treatment showed a significant difference in the two groups (VAS: Group A difference of 4.3, Group B difference of 3.1, $p = 0.005$; dyspareunia: Group A and Group B 1.8 vs. 0.8, $p = 0.005$). **Conclusion:** The positive results of our study prove the utility effectiveness of an enzyme combination to decrease and normalize the biomarkers of inflammation in VBD and PBS patients in a multimodal approach.

Keywords: Vulvodynia; TENS; Vulvar Vestibulitis Syndrome; Painful Bladder Syndrome; Immunoenzymatic Therapy

1. INTRODUCTION

The International Society for the Study of Vulvovaginal Disease defines vulvodynia as “vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder” [1].

It is classified according to the site of pain, whether generalized or localized and whether provoked, unprovoked or mixed [1].

Vestibulodynia (VBD) defines the most common localization, which is at the vulval vestibule, and it was estimated that it affects at least 16% of women in the United States [2].

Interstitial cystitis (IC) is a chronic syndrome characterized by the symptoms of urinary urgency/frequency, pelvic pain and nocturia, in the absence of bacterial infection or any other identifiable pathology [3].

To be more inclusive of patients with this symptom complex, the nomenclature is evolving to also include bladder pain syndrome or painful bladder syndrome (PBS) [4].

Patients with IC/PBS or vulvodynia may present symptoms such as chronic pelvic pain, vulvar pain and/or dyspareunia.

Several case studies have described patients who have both conditions concurrently and among women with urologist-diagnosed IC/PBS more than half can be diagnosed with vulvodynia [5,6].

There may be a common etiology for these two conditions. The vulva and bladder are both derived from the embryonic urogenital sinus and share common sacral nerve innervation pathways [7]. Conditions that affect the bladder may therefore lead to symptoms in the vulva and vice versa.

The pathogenesis of IC/PBS and vulvodynia are not completely understood but it is thought to be multifactorial.

The theory of a neuropathic disorder involving abnormal pain perception is now prevailing.

Two elements are common in the two diseases: an increased number of activated mast cells located close to nerves with enhanced levels of pro-inflammatory cytokines and histologic examinations, have revealed that the

affected mucosa (vulvar vestibule and bladder wall) has hyperinnervation in the stroma and epithelium [8,9].

Given the range of symptoms associated with vulvodinia and PBS/IC and the possibly multifactorial etiology, the best approach to treatment is a multimodal one that can be tailored to each patient.

Many therapeutic approaches are proposed for the two diseases. One of the more effective for the treatment of VBD is transcutaneous electric nerve stimulation (TENS) while the systemic pharmacological approach is preferred for IC/ PBS [2,10].

Amitriptyline and gabapentin/pregabalin are commonly used both for the therapy of PBS and VVS. Wobenzym vital[®] is an enzymatic combination of papain, bromelain, trypsin, chymotrypsin and quercetin, substances with regulatory action on the pool of cytokines and mast cell activity. Objective of the study was to assess the effectiveness of Wobenzym vital[®] in the supportive treatment of VBD/PBS patients undergoing TENS + amitriptyline and pregabalin therapy as a multimodal treatment strategy.

2. MATERIAL AND METHODS

Forty women entered the study. All were diagnosed as having vestibulodynia due to the coexistence of the following conditions: a history of at least 6 months of vulval pain upon tampon insertion or attempted intercourse and a positive cotton-swab test, that is, tenderness at palpation of the vestibular area with a cotton tip applicator [11], associated with a PBS with symptoms of urinary urgency, frequency, and pelvic pain who had identifiable causes ruled out such as urinary tract infections or bladder cancer [9].

A randomized controlled trial was performed to study the efficacy of two regimens of treatment for VBD associated to PBS.

Randomisation was determined by a computer generated number list. Institutional Review Board approval for the study was obtained and all participating individuals were given written informed consent.

Patients were randomly assigned to receive a systemic therapy according to the following protocol:

-Group A: amitriptyline + Pregabalin.

-Group B: amitriptyline + Pregabalin *plus* a systemic enzyme preparation containing papain, bromelain, trypsin, chymotrypsin and quercetin (Wobenzym vital[®]).

The amitriptyline dose was typically started at 6 mg nightly and was titrated by 6 mg nightly every week for individual patients, on the basis of the tolerance of adverse effects and pain relief. Pregabalin was started at 25 mg twice daily and it was increased to 50 - 75 mg twice daily within two weeks based on efficacy and tolerability.

Wobenzym vital[®] at two tablets two times a day was

added in the second group of patients.

All patients received TENS therapy in a self-administered domiciliary protocol. A dual channel portable TENS unit (NeuroTrac[™] Continece-Verity Medical UK) was used, which produces a symmetrical biphasic wave and has three customizable mode programs. The stimulation was delivered through a commercially available plastic vaginal probe (Novaty-Gold), 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 study [12]. The standard protocol for TENS was 15 min of 10-Hz frequency and pulse duration of 50 microseconds (first program), followed by 15 min of 50-Hz frequency and pulse duration of 100 microseconds (second program). All patients received a supervised TENS trial of TENS prior to use at home. The trial consisted in 6 - 7 sessions, which served to familiarize the patient on use of TENS, while allowing the therapist to check that the patient was using the device properly.

In the TENS treatment protocol the pulse is increased rapidly until the patient reports the onset of any sensation under the electrodes. The intensity is then increased slowly until this sensation reaches a level described as the maximum tolerable, without experiencing pain.

After completing the trial, the patient is consigned their TENS unit after verbal and written instruction, with a recommendation to perform home treatment three times each week.

Clinical response from baseline to week eight after starting treatment was assessed by outcome measures including change in daily pain intensity and change in urinary urgency and frequency. Symptoms of irritation and burning were assessed on a 10-cm visual analogue scale (VAS) and dyspareunia was recorded and graded on a 0 - 3 score according to the Marinoff Dyspareunia Scale [11].

The characteristics of the study population are summarized in **Table 1**. Women in the two groups were similar in age, parity, and symptoms at recruitment into the study.

The EPI-INFO version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA) was used for all statistical analyses. Descriptive statistical analysis (means, SDs and percentages) was performed using Student's t-test and ANOVA. Significance is taken at $p < 0.05$.

3. RESULTS

Patients received a mean of 24.8 (range 21 - 35) TENS sessions, without significant differences between the two groups (Group A: mean 22 sessions; Group B: mean 21 session).

The average dose of amitriptyline and Pregabalin in

Table 1. Characteristics of the study populations.

	Group A	Group B	P value
Age (years)	30 (21 - 44)	26 (21 -35)	NS
Nulliparous	18/20 (90%)	19/20 (95%)	NS
Duration of Symptoms (months)	8.4 (3 - 48)	14.1 (7 - 23)	NS
Sexually Active	17/20 (85%)	18/20 (90%)	NS
VAS	6.2 ± 1.9	6.7 ± 2.0	NS
Marinoff Dyspareunia Scale	2.7 ± 0.4	2.7 ± 0.4	NS

Values are means and ranges or ±1SD, or numbers and percentages.

group A were respectively 16 mg (range 6 - 30 mg) and 50 mg (range 25 - 150 mg), while in group B is assessed at 14 mg respectively (range 6 - 28 mg) and 50 mg (range 25 - 150 mg); no significant differences between the two groups were found ($p = 0.08$).

All scores in the two groups improved significantly by the end of treatment compared with pre-study values.

The VAS baseline and after two months of treatment showed a significant difference in the two groups: Group A difference of 4.3, Group B difference of 3.1 ($p = 0.005$).

The same was demonstrated for the score tied at dyspareunia: Group A and Group B 1.8 vs. 0.8 ($p = 0.005$).

The overall incidence of adverse events was very low, and none led to treatment discontinuation. Adverse events were reported in 4 patients: mild and transient gastrointestinal symptoms, none leading to withdrawal and dropout.

4. DISCUSSION

The results reported here are consistent with our recent randomized, controlled trial demonstrating that TENS is an effective treatment for vestibulodynia [12].

Hypotheses for the etiology of vulvodynia include neuropathic mechanisms, neural hyperplasia, neurogenic inflammation, abnormal local and/or central nociception, abnormal neurosecretion of neurotransmitters and neuropeptides, pelvic muscle hypertonicity, with a multiple combination of these processes.

An inflammatory process in the vulvar vestibule can release a cascade of cytokines that sensitize the nociceptors and induce nerve growth factors resulting in a physical increase in the number of nerves and an increase in local nociceptors. The local sensory pain nerves become progressively more sensitized, and develop abnormal neurosecretion, worsening the problem. It appears that some patients with localized vulvodynia have an interleukin-1 beta polymorphism that modulates inflammation and pain, resulting in further hyperpathia/allodynia (pain in response to a normally nonpainful stimulus) [8].

When there is prolonged activation of the nerve fibers to the dorsal root ganglion, chronic release of neuroactive substances occurs and more nerves are stimulated, resulting in “central sensitization.” This leads to a functional reorganization of the dorsal horn in the spinal cord resulting in remodeling of the central processing of pain signals.

Central and peripheral sensitizations seem to be responsible for perpetuation of the symptoms long after any “triggering factor” has been resolved.

Evidence is growing that VBD and PBS should be considered part of a visceral pain syndrome and neurogenic inflammation with a neural sensitization may be the primary source of pain.

Given the range of symptoms associated with VBD and PBS and the possibly multifactorial etiology, the best approach to treatment is a multimodal one that can be tailored to each patient.

TENS, amitriptyline and pregabalin act both by enhancing dorsal horn inhibition and by diminishing peripheral and central sensitization.

The therapeutic neuromodulation to TENS is based on presynaptic inhibition in the dorsal horn of the spinal cord, on direct inhibition of an abnormally excited nerve, on restoration of afferent input explained by the “gate control theory” [13].

Contextually, electrical stimulation delivered by a TENS unit activates sovraspinal inhibitory systems and it increases the release of endogenous morphine-similar substances (amplification of endogenous Descending System for Analgesia) [14].

We believe that another important target of therapy is represented by neurogenic inflammation.

The body also creates cytokines as a response to inflammation. Cytokines act as chemical messengers bring white blood cells, particularly mast cells, to inflammation areas. Some cytokines also increase inflammation (Th1), while others control inflammation (Th2).

In VBD patients we can find an imbalance of pro-inflammatory cytokines, and similar alterations can be found in the bladder wall of women with PBS.

A similar enzyme combination as in Wobenzym vital[®] has been shown to decrease and normalize the biomarkers of inflammation like the normalization of cytokine levels [15].

The binding and removal of excessive cytokines is mediated by α -2-macroglobulin (alpha 2-macroglobulin), a naturally occurring high molecular weight plasma glycoprotein. Proteases bind with α -2-macroglobulins to create α -2-macroglobulin-protease and transform the α -2-macroglobulin from its native form into the active form [16].

Systemic enzyme supports increases endogenous proteases and supports the activation of α -2-macroglobu-

lin.

It is again important to note that quercetin, substance contained in Wobenzym vital[®], is a compound shown to inhibit differential release of IL-6 in response to IL-1 by reducing intracellular calcium ions [17].

An interesting observation in this clinical study on vestibulodynia + PBS involves the relatively short duration of the disease (<eight months).

These data are supported by the fact that the cytokine levels in/of mast cells in inflamed tissue change over time.

In tissue where there is an acute inflammatory response, as seen in an early stage of disease, the cytokine levels are significantly increased in the vestibular mucosa; as the inflammation becomes more chronic, the cytokine levels cells decreases and there is a proliferation of C-afferent nociceptors in the vestibular mucosa.

At this late stage of the inflammatory process neuro-pathic symptoms, such as hyperalgesia and allodynia, became prominent and the neuropathic pain in stabilized.

For the above considerations the results reported in the present study demonstrate the synergic action of Wobenzym vital[®] when the disease has a recent onset.

Furthermore combination therapy should preferably use drugs with complementary mechanisms. Finding an effective therapy for an individual patient with vestibulodynia can be quite time consuming and some of the treatments, such as amitriptyline, produce systemic side effects such as drowsiness which may limit their use. The synergistic interactions between amitriptyline and Pregabalin are not only logical but also encouraged by a reduction of side effects by the use of lower doses.

The results presented here may be criticized because of the short follow-up. They should be confirmed with larger studies. Our results highlight the need for future trials which focus on triggers of neural hyperplasia that originate in cytokine levels. Hopefully a larger study with a longer follow-up will permit a more detailed analysis and understanding of which patients are more likely to improve with this treatment synergy.

REFERENCES

- [1] Moyal-Barracco, M. and Lynch, P.J. (2004) ISSVD terminology and classification of vulvodynia: A historical perspective. *The Journal of Reproductive Medicine*, **49**, 772-777.
- [2] Haefner, H.K., Collins, M.E., Davis, G.D., Edwards, L., Foster, D.C., Hartmann, E.D., *et al.* (2005) The vulvodynia guideline. *Journal of Lower Genital Tract Disease*, **9**, 40-51. [doi:10.1097/00128360-200501000-00009](https://doi.org/10.1097/00128360-200501000-00009)
- [3] Butrick, C.W. (2003) Interstitial cystitis and chronic pelvic pain: New insights in neuropathology, diagnosis, and treatment. *Clinical Obstetrics and Gynecology*, **46**, 811-823. [doi:10.1097/00003081-200312000-00011](https://doi.org/10.1097/00003081-200312000-00011)
- [4] Van de Merwe, J.P., Nordling, J., Bouchelouche, P., *et al.* (2007) Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: An ESSIC proposal. *European Urology*, **53**, 60-67.
- [5] McCormack, W.M. (1990) Two urogenital sinus syndromes: Interstitial cystitis and focal vulvitis. *The Journal of Reproductive Medicine*, **35**, 873-876.
- [6] Peters, K., Girdler, B., Carrico, D., *et al.* (2008) Painful bladder syndrome/interstitial cystitis and vulvodynia: A clinical correlation. *International Urogynecology Journal and Pelvic Floor Dysfunction*, **19**, 665-669.
- [7] Myers, D.L. and Aguilar, V.C. (2002) Gynecologic manifestations of interstitial cystitis. *Clinical Obstetrics and Gynecology*, **45**, 233-241. [doi:10.1097/00003081-200203000-00024](https://doi.org/10.1097/00003081-200203000-00024)
- [8] Bornstein, J., Goldschmid, N. and Sabo, E. (2004) Hyperinnervation and mast cell activation may be used as histopathologic diagnostic criteria for vulvar vestibulitis. *Gynecologic and Obstetric Investigation*, **58**, 171-178. [doi:10.1159/000079663](https://doi.org/10.1159/000079663)
- [9] Metts, J.F. (2001) Interstitial cystitis: Urgency and frequency syndrome. *American Family Physician*, **64**, 1199-1206.
- [10] Friedrich Jr., E.G. (1987) Vulvar vestibulitis syndrome. *The Journal of Reproductive Medicine*, **32**, 110-114.
- [11] Marinoff, S.C. and Turner, M.L.C. (1992) Vulvar vestibulitis syndrome. *Dermatologic Clinics*, **10**, 435-444.
- [12] Murina, F., Bianco, V., Radici, G., Felice, R., Di Martino, M. and Nicolini, U. (2008) Transcutaneous electrical nerve stimulation to treat vestibulodynia: A randomized controlled trial. *BJOG: An International Journal of Obstetrics & Gynaecology*, **115**, 1165-1170. [doi:10.1111/j.1471-0528.2008.01803.x](https://doi.org/10.1111/j.1471-0528.2008.01803.x)
- [13] Paxton, S. (1980) Clinical use of TENS: A survey of physical therapists. *Physical Therapy*, **60**, 38-44.
- [14] Robinson, A.J. and Snyder-Mackler, L., Eds. (2008) Clinical electrophysiology. Lippincott Williams & Wilkins, Philadelphia, 107-149.
- [15] Lauer, D., Reichenbach, A. and Birkenmeier, G. (2001) Alpha 2-macroglobulin-mediated degradation of amyloid beta 1-42: A mechanism to enhance amyloid beta catabolism. *Experimental Neurology*, **167**, 385-392. [doi:10.1006/exnr.2000.7569](https://doi.org/10.1006/exnr.2000.7569)
- [16] Mettenburg, J.M. and Gonias, S.L. (2005) Beta-amyloid peptide binds equivalently to binary and ternary alpha2-macroglobulin-protease complexes. *The Protein Journal*, **24**, 89-93. [doi:10.1007/s10930-004-1515-7](https://doi.org/10.1007/s10930-004-1515-7)
- [17] Kandere-Grzybowska, K., *et al.* (2006) Regulation of IL-1-induced selective IL-6 release from human mast cells and inhibition by quercetin. *British Journal of Pharmacology*, **148**, 208-215. [doi:10.1038/sj.bjp.0706695](https://doi.org/10.1038/sj.bjp.0706695)