

VULVAR VESTIBOLITIS: TREATMENT WITH OXYGEN THERAPY AND HYALURONIC ACID

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Vestibulitis Vulvar (VV) is a chronic, heterogeneous, multifactorial and multi-systemic disease. Friederich first described it in 1987 as a disease characterized by the presence of three particular symptoms and signs:

1. severe pain upon contact with the vaginal vestibule and dyspareunia;
2. fragility of the vestibular tissue, evident on contact;
3. objective finding of vestibular erythema of different degrees.

It is the main cause of dyspareunia in women of childbearing age and affects 8-12% of women who go to a gynecological clinic.

As a multi-systemic disease, VV has a complex pathophysiology. Bornstein demonstrated that the mucosal structure of the vestibule is susceptible to a mast cell-mediated inflammatory response. In the population affected by VV, in fact, a significantly higher number of mast cells can be found in the superficial layers of the vestibular mucosa than in the deep ones and, in parallel, a significant increase in the production, deposition and release of multiple inflammatory mediators. Chronic inflammation could therefore be responsible for the thinning and friability of the introital mucosa typical of VV.

The up-regulation of mast cells increases the production of cytokines, substance P and other inflammatory mediators that cause vasodilation, transudation, edema, swelling, redness and pain. The production of Nerve Growth Factor (NGF) by the hyperactive mast cell stimulates the proliferation of pain nerve fibers, which by extending to the most superficial layers of the mucosa cause both an increase in pain perception (hyperalgesia) and a perceptual change in pain tactile type to one characterized by burning (allodynia).

The activation of mast cell degranulation is mediated in different ways and times by different agonist stimuli that contribute to the heterogeneity of the clinical presentation. Infections (primarily from *Candida albicans*, present in 58.1% of women with VV in personal cases, against a prevalence of 5-8% in the general population), mechanical trauma from rubbing during intercourse, if lubrication was insufficient, estrogen, chemical and physical stimuli, allergens can all activate the release of mast cell mediators. They can promote inflammation by showing its typical clinical

characteristics (rubor, tumor, calor, dolor et functio laesa, understood as the impossibility of sexual intercourse).

The first symptom of VV is acute (nociceptive) pain, caused by the intercurrent inflammation and the injury from which the body tries to react and adapt. Over time, the pain can become chronic and itself become a disease (neuropathic), being generated by the nerves themselves or by the higher centers. The up-regulation of the pain system stimulates the adrenergic system by inducing the activation of the autonomic nervous system responsible for pain hyperesthesia, any defensive posture and changes in the pain threshold.

The pain often causes a defensive contraction of the muscles in the affected area to minimize further injury. The contraction of the levator ani may also pre-exist VV, if associated with vaginismus as a predisposing factor, or acquired in response to persistent introital pain. Recent research suggests that the difficulty in inserting internal tampons, in adolescents, could be the symptom of an hyperactivity of the levator ani muscle, which causes an excessive contraction of the same such as to restrict (reversibly) the vaginal entrance. This hypertonicity would become a predisposing factor both to make penetration persistently painful from the beginning of sexual life ("lifelong", or primary dyspareunia) and to cause microtrauma of the vestibule in the event of sexual intercourse, then precipitating the VV.

As for the involvement of the hormonal system, VV is a typical disorder of the fertile age. Premenstrual pain attacks ("flares") are typical in some women. Hypersensitivity of the mast cell to estrogen has been hypothesized. Estrogens are in fact agonists of mast cell degranulation. After menopause, recurrences of VV were found during vaginal and / or systemic hormone replacement therapy, in synergy with recurrent candidiasis. This is due to the interaction between estrogen and vulnerability to candida infections, and between estrogen and mast cell degranulation.

The vascular system is activated during chronic inflammation. Vestibular erythema is the epiphenomenon of superficial vasodilation mediated by the peptide of the calcitonin gene (CGRP) released by nociceptors C which can cause vasodilation and activation of the axonal reflex even at low levels of activity. Neurogenic inflammation describes acute vasodilation mediated by nerve signals that move retrograde along the sensory nerves and could activate both degranulation and vasodilation.

Diagnosis

VV should be suspected: a) when a woman complains of superficial dyspareunia, with burning and / or acute pain, on introital contact; b) when the three signs described by Friederich are found on clinical examination. Instrumental examinations are currently mainly used in research.

Anamnesis

1) General medical evaluation, which includes, in addition to the traditional medical history, particular attention to recording:

- pelvic medical comorbidities: urological disorders of the lower urinary tract, relapsing cystitis, interstitial cystitis, urinary urgency, enuresis; iatrogenic vaginal pains (outcomes of episiorrhaphy, colpoplasty, especially if posterior, of radical vaginal surgery and / or pelvic radiotherapy); constipation, fissures, hemorrhoids;
- systemic comorbidities: for example diabetes, as it favors relapsing candida infections; infections, also in other organs, which require repeated antibiotic therapies, which often result in recurrent candida infections; allergies and atopies; depressions¹⁵;
- previous or current vaginal infections, or sexually transmitted diseases such as candida, gardnerella, HPV and genital herpes, which deserve specific attention from the doctor, as predisposing or precipitating factors for VV. If so, the vaginal environment should then be evaluated with a vaginal swab and a culture test, especially in the suspected infectious;
- all current or previous pharmacological treatments aimed at treating both other conditions and VV. Any ongoing hormonal treatment (oral contraceptive therapy, hormone replacement, etc.), and all systemic and local treatments should therefore be documented.

2) Sexological anamnesis focused on any dysfunctions prior to the appearance of VV^{15, 16}. A woman's sexual practices, and the coexistence of any sexual dysfunction, primary ("lifelong") or acquired (secondary), concerning possible dysfunctions of desire, excitement, orgasm and dyspareunia must be investigated and recorded. In young women, the possible symptoms associated with VV, including difficulty in using vaginal tampons and fear of penetration, as well as any post-coital urinary symptoms (cystalgia and / or postcoital urethralgia, dysuria, urge urination) deserve particular attention. ;

3) A woman's perception of the duration and characteristics of the symptoms, that is, how the disease is experienced both as physical suffering and as an interaction with affective, work and social activities.

Physical examination

It should document:

- the presence of general defensive postures (ie characterized by an excessive increase in general muscle tone and the refusal of any genital contact, including vaginal physical examination) and primary dyspareunia. These signs and symptoms may be associated with primary vaginismus concomitant with VV.
- The evaluation of the vaginal pH, tested with a vaginal stick during the gynecological examination, since it must always be recorded in the file.
- The quality of the pain. During the gynecological examination, three basic questions should be reformulated regarding: "Where does it hurt?", "When does it hurt?" and "What symptoms accompany the pain?". These three questions are essential: location and onset characteristics of pain are in fact the strongest predictors of the biological etiology of pain itself and should introduce the next step regarding the objectification of clinical data^{17,18}.

- Pain mapping: precise identification of points of tenderness at the level of the external genitalia, the middle and distal vaginal third 17,18. The precise localization of pain, its beginning, its characteristics are the main predictive signs of its organicity.
- The quantization (score) of pain. It involves bilateral quantification of the perception of pain intensity using the Likert visual analog scale (from 0: no pain to 10: pain of a more intense degree).

COMBINED USE OF OXYGEN AND HYALURONIC ACID IN THE TREATMENT OF VESTIBOLITIS: CASE STUDY

For the treatment of vestibulitis, oxygen therapy was chosen as the use of this technique satisfies the treatment of symptoms such as: recurrent infections, burning, pain and dyspareunia that characterize this disease.

Oxygen therapy has a powerful regenerative, antibacterial and biostimulating effect, it is therefore believed that the treatment of symptoms such as itching and burning can also be very useful in the treatment of this pathology. Oxygen therapy increases the availability of oxygen to the tissues, promotes the increase in tissue repair processes and increases the synthesis of collagen allowing normal hydroxylation of this protein. In fact, at tissue oxygen tensions lower than normal, collagen is not synthesized correctly, slowing the healing of ulcers and wounds. In addition, oxygen induces a neo-angiogenic stimulus by releasing factors such as the Vascular Endothelial Growth Factor (VEGF). This function is essential for the restoration of the microcirculation in compromised vascular situations, re-establishing a vascular flow in the hypoxic areas that guarantees correct tissue regeneration.

Hyaluronic acid is a natural polysaccharide that forms a fundamental part of the extracellular matrix of the skin and cartilage. Hyaluronic acid: has remarkable adhesive, moisturizing and reparative properties of the vaginal mucosa.

The association of high concentration oxygen and hyaluronic acid has been shown to have therapeutic efficacy in the treatment of vulvo-vaginal atrophy, the aim of the study is to use the association between high concentration oxygen and hyaluronic acid for treatment. of the disorders caused by vestibulitis and the improvement of the quality of life of people affected by this pathology.

Treatment

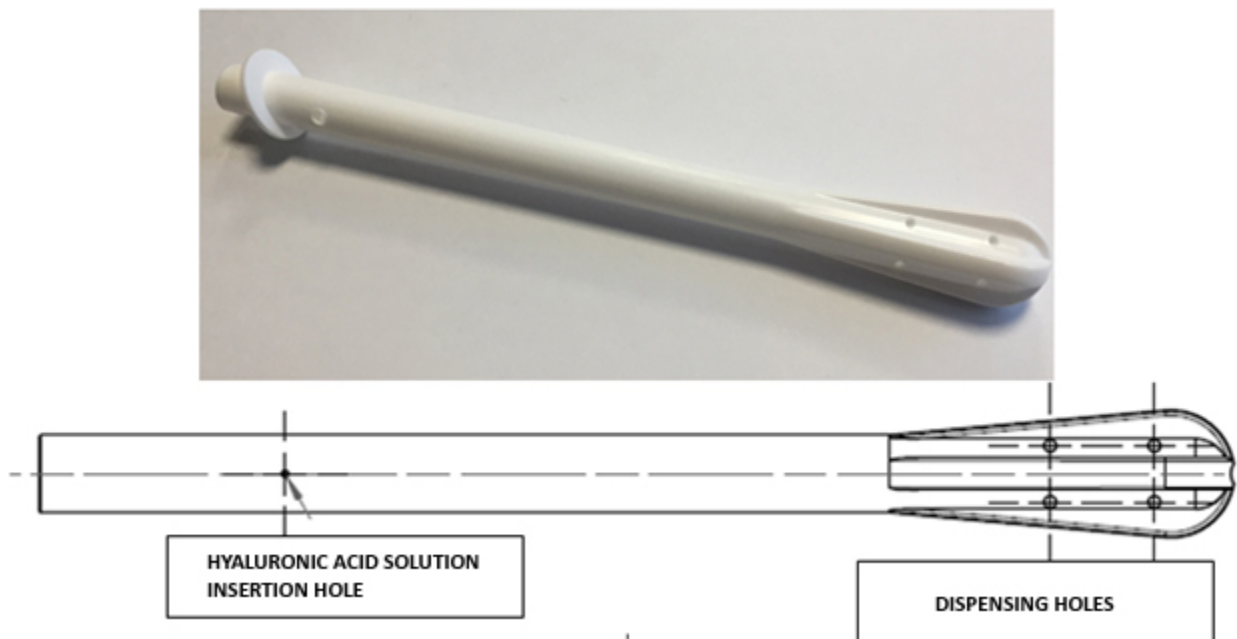
Five weekly oxygen therapy treatments were performed on 25 women diagnosed with vestibulitis, for a total of five weeks. La terapia ambulatoriale era così composta: erogazione di ossigeno e acido ialuronico nebulizzato con applicatore vulvare, per una durata di cinque minuti. Successivamente è stata applicato ossigeno vaginale per 10 minuti e erogazione di ossigeno e acido ialuronico per ulteriori 5 minuti.

For the treatment, the Caress Flow system was used, an oxygen therapy device for gynecological use that allows the topical administration of oxygen with a high degree of purity up to $93 \pm 3\%$, at a flow of 1-6 l / minute.

The device consists of a compressor that generates compressed air by sucking air from the external environment, filtering and compressing it. Inside the machine body there are zeolite molecular sieves that exploit the principle of the different absorption of gas molecules, letting the O₂ pass and retaining the other gases present in the air, such as nitrogen, argon, helium and hydrogen. The machine body transforms the outside air into $93 \pm 3\%$ pure oxygen.

Two dispensers were used, the first consisting of a vaginal cannula, connected to the machine body. The cannula is equipped with outlet holes for the delivery of oxygen and hyaluronic acid, which is inserted through a special insertion hole located in the upper part of the cannula (Figure 1). The vaginal cannula is used for treatment inside the vaginal canal.

FIGURE 1



In addition to the cannula, an airbrush was used (Figure 2), always connected to the machine body, capable of delivering oxygen in combination or not with the hyaluronic acid solution. The airbrush is used for the treatment of the external genitalia, nebulizing the combination of oxygen and hyaluronic acid.

Hyaluronic acid is previously dissolved in distilled water, to form a 0.2% (w / v) solution.

FIGURE 2



All patients have pelvic muscle hypertonus, in addition to vulvar and vaginal oxygen therapy, a manual physiokinesitherapy treatment was applied after the delivery of oxygen and hyaluronic acid with the aim of treating pelvic contracture.

A double evaluation was performed on the treated subjects: one subjective by the patients and one by the doctor. The subjective scale was compiled using an analog graded card that assessed pain during sexual intercourse (dyspareunia), dryness, itching and burning with a VAS scale from 0 to 10, where 10 represents the maximum intensity and 0 the absence of the disorder, analyzing the symptoms before the first treatment session (T0) and at the end of the 5 sessions (T5). Instead, the pH, elasticity, tone and the presence or absence of infections were evaluated by the doctor (Table 1).

TABLE 1

	Absent	Mild	Moderate	Strong	
SCORE	0	1--2--3	4--5--6	7-8-9-10	
	Absent	Poor	Mean	Good	Excellent
ELASTICITY	1	2	3	4	5

Results

Patients reported significant improvement in all indices analyzed (Figure 3), with the greatest effect in pain reduction (VAS T0 = 7.2; VAS T5 = 1.5, Wilcoxon signed-rank test $P < 0.0001$), but also with regard to burning (VAS T0 = 7.28; VAS T5 = 1.48, Wilcoxon signed-rank test $P < 0.0001$) and pruritus (VAS T0 = 6.64; VAS T5 = 1.36, Wilcoxon signed-rank test $P < 0.0001$).

As regards the elasticity index, the variation between T0 and T5 appears highly significant (Wilcoxon signed-rank test $P < 0.0001$) with an increase in the index from 2.48 to 4.48.

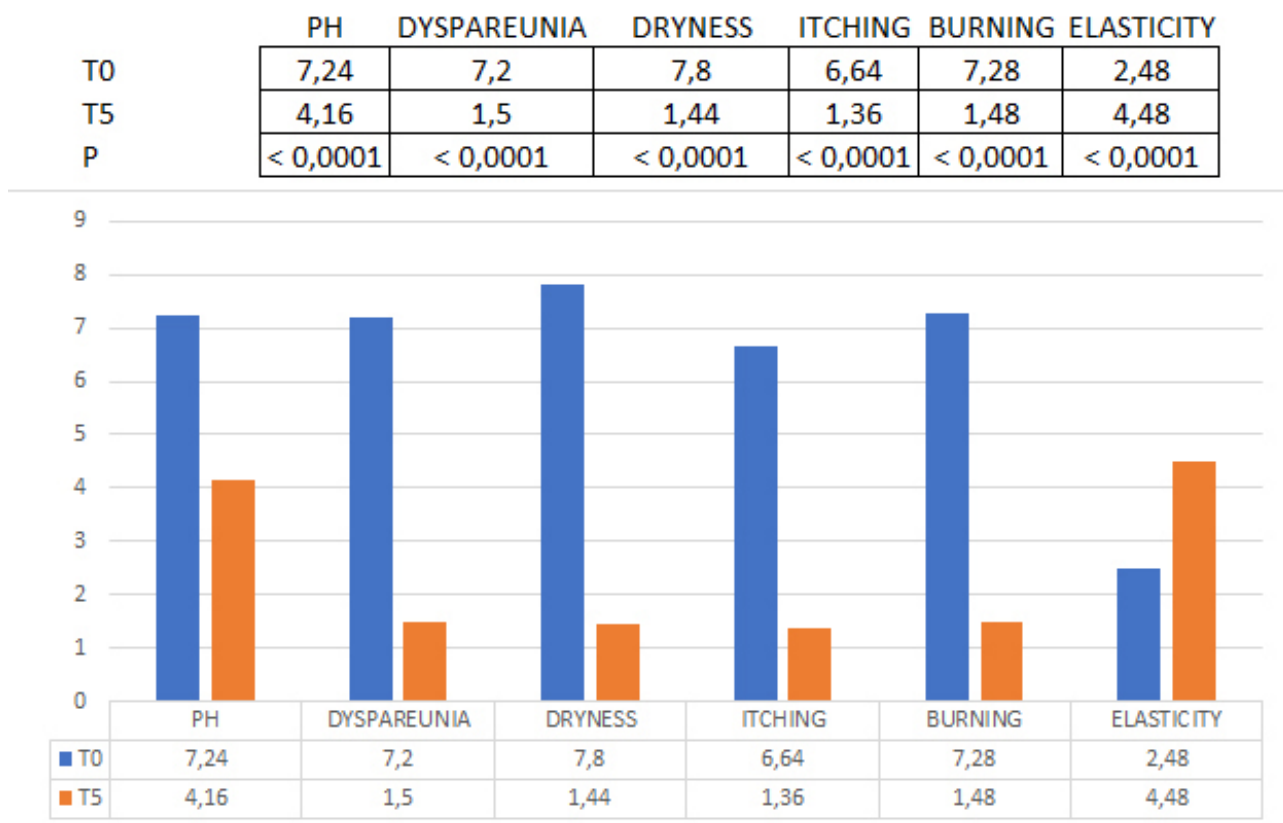


FIGURE 3

The data regarding the effect of the treatment on tone show that in all cases there was an improvement in symptoms (Table 2).

Of the 25 women included in the trial, 18 had T0 infections, confirming the association between vestibulitis and vulnerability to candidiasis. At the end of treatment (T5) all detected infections were resolved (Table 2), demonstrating the effectiveness of the combined treatment of high concentration oxygen and hyaluronic acid.

No side effects associated with the treatment were reported by the patients.

	TONE		INFECTIONS	
	T0	T5	T0	T5
1	over	normal	Candidiasis	no
2	over	normal	Candidiasis	no
3	over	normal	Candidiasis	no
4	over	normal	Candidiasis/Cystitis	no
5	over	normal	Candidiasis	no
6	over	normal	Candidiasis	no
7	over	normal	Candidiasis	no
8	over	normal	Candidiasis	no
9	over	normal	Candidiasis	no
10	normal	normal	\	\
11	over	normal	\	\
12	over	normal	Cystitis	no
13	over	normal	Candidiasis	no
14	over	normal	Candidiasis/Cystitis	no
15	over	normal	\	\
16	over	normal	\	\
17	over	normal	Candidiasis	no
18	over	normal	Candidiasis	no
19	over	normal	Candidiasis	no
20	over	normal	Candidiasis	no
21	over	normal	\	\
22	over	normal	\	\
23	over	normal	\	\
24	over	normal	Candidiasis	no
25	over	normal	Candidiasis	no

TABLE 2

Combined oxygen therapy with hyaluronic acid has proven to be a valid method for treating the symptoms associated with vestibulitis. It is a totally painless therapy, with excellent compliance by patients. It is a fast, non-invasive and repeatable treatment, with no side effects.