







Relapsing Vulvovaginal Candidiasis: Treatment with Oxygen Therapy and Hyaluronic Acid

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Abstract

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BACKGROUND: Vulvovaginal candidiasis (VVC) is a common fungal infection caused by *Candida* species. It affects about 138 million women per year worldwide. Several clinical studies confirmed that hyaluronic acid administration has vaginal estrogens-like effects, relieving the typical vaginal atrophy symptoms, including dryness, itching, and dyspareunia. Local oxygen therapy, on the other hand, has a powerful regenerative, antibacterial, and biostimulating effect.

AIM: The aim of our open, anecdotal, retrospective, and spontaneous trial has been to evaluate the efficacy of the association between high concentration oxygen and hyaluronic acid for treatment of relapsing candidiasis.

MATERIAL AND METHODS: Forty-five women (30.9 ± 4.4 years) with relapsing candidiasis, and complaining of dryness, dyspareunia, pain, appealing to our Second Opinion Medical Consultation Network, signed an informed consent form and were treated with oxygen/hyaluronic acid therapy treatment, once a week, for total of 5 weeks at the outpatient clinic (Healthy Center, Sirio, Fidenza, Italy). The physicians of the Second Opinion Network followed up weekly from remote (WhatsApp, Skype) each treated patient as to state the effectiveness, tolerability, and side effects of the treatment.

RESULTS: The mean VAS and VuAS scores measured at first visit were 2660 and 2622 and significantly ($p < 0.0001$) reduced to 1,311 and 0.77 at last visit. The measurements of the vaginal pH and of the vaginal swab after the last treatment session confirmed significantly ($p < 0.0001$) the absence of candidiasis. Three months later in the follow-up, the percentage of patients who had had only one VVC relapse was 4.44% (2/45), a percentage that increased just to 8.8% at six months (4/45). The elastography index was significantly ($p < 0.0001$) increased after the last treatment session (2.55 ± 0.545 vs. 4.48 ± 0.505).

CONCLUSION: The combined oxygen therapy with hyaluronic acid gave definite therapeutic benefits in this cohort of relapsing candidiasis in the acute phase of the infection. The 6-month follow-up, also detected a lower reinfection rate compared with the historical available data. The procedure is totally painless with excellent compliance by patients and no untoward effects.

Introduction

Vulvovaginal candidiasis (VVC) is a common fungal infection caused by *Candida* species [1], [2]. It affects about 138 million women (between 25 and 34 years old) per year worldwide [3], [4]. The number of women with recurrent disease is supposed to increase to almost 158 million in 2030 [3]. About 70–75% of women, especially of childbearing age, have VVC infection at least once in their life and 40–50% relapse [5]. In fact, about 20% of acute infections turn in relapsing mycotic vulvar-vaginitis, four or more times in a year [6]. The *Candida albicans* strain affects 85% of the women, relapsing in about 5% of the infections [1]; however, in the last years further pathogenic species, such as *Candida glabrata*, *Candida krusei*, and *Candida tropicalis*, have emerged [7]. All these strains in a balanced saprophytic environment are normal commensals of the microbiota either in the vaginal

cavity or in other warm-humid body surfaces [1]. In fact, the *Candida* species, in particular *Candida albicans*, are ubiquitous pathobiotic microorganisms, members of commensal flora, which can cause infections in healthy and immunocompromised people when an imbalance between microbial-related factors (virulence factors) and host-related factors occurs [8], [9]. The main virulence factors include: the morphological transition from yeast to hyphal form [10], the expression of cell surface molecules, such as adhesins, to help the *Candida* to adhere to epithelial cells [11], directional hyphal growth (thigmotropism) [12], the biofilm formation [13], phenotypic switching, the secretion of extracellular hydrolytic enzymes such as proteinases and phospholipases [14], the ability to change its morphology [15], and its metabolic adaptability [16]. Through these virulence factors, *Candida* spp. can adapt to different host niches and cause infections. Other factors include rapid adaptation to fluctuations in environmental pH, mediated by heat shock proteins

(Hsps) [17]; auto-induced hyphal formation through selective amino acid and metals, such as carbon, nitrogen, iron, zinc, or copper uptake can influence the fungal pathogenicity [18].

Diagnosis of relapsing candidiasis can be quite puzzling due to the non-striking symptoms, the inconspicuous objectivity, and the positivity of the culture examination only in 20–30% of cases but being a widespread public health problem, it has a heavy medical and socio-economic burden [14], [19].

The symptoms are pruritus, soreness, irritation, vaginal discharge, and discomfort, while the clinical signs are introital/vulvar and vaginal erythema, edema, excoriation, typical leukorrhea, vulva and vaginal burning, dysuria, dyspareunia, and frequent micturition [20], [21], [22]. The patients also report reduced fitness and physical activities, with psychological involvement in terms of anxiety, depression, and loss of self-esteem [3], [20].

The moderately acidic (range: 3.8–5.0) normal vaginal pH prevents vaginal infections but several factors, such as age, nutrition, and vaginal Hydration *et al.* can modify it [23], [24]. Consequently, a high vaginal pH level (greater than 5) suggests bacterial vaginosis, trichomonas vaginitis, or candidiasis [25], [26].

Candidiasis is also frequent in pregnant women and can be transmitted to the new-born during delivery or in the postnatal phase, requiring clinical protocols for prevention [27].

The relapse episodes can be due to recurrent oropharyngeal candidiasis in patients with advanced and uncontrolled HIV infection, to genetic factors (polymorphism, familial, and ethnicity), to immune mechanisms (uncontrolled diabetes, antibiotics, and hormone replacement therapy), to behavioral reasons (oral sex, oral contraceptive, corticosteroids, hormonal changes, and intercourse frequency), to psycho-emotional changes, to inadequate intimate hygiene or clothes inducing sweat and local heat in the vulvovaginal area, and to idiopathic factors [28], [29], [30], [31], [32], [33].

The use of topic and oral antifungals, such as nystatin, fluconazole, azole and triazole derivatives, is generally safe and well tolerated, but can promote, especially fluconazole, in the long run, progressive drug resistance by the *Candida* strains [34], [35], such as *C. glabrata* and *C. krusei* [36], which are more pathogenic in terms of edema, skin irritability, and chronic vulvar pain (vulvodinia) [37], [38]. In fact, in the last decade, different women with recurrent VVC appeared fluconazole resistance [39]. Some other less used but effective drugs, including polyenes and echinocandins induce also substantial toxicity [40], [41], [42].

Considering these limitations and the continuous increase of Candidiasis incidence, semi-solid mucoadhesive formulations, such as gel with propolis, have been proposed [43], [44], but new more effective, safe and cheaper drugs and strategies are

required to treat this infection, especially the recurrent cases.

Farida *et al.* [45] analyzed the beneficial effect of Indonesian Propolis wax, as anti-candida agent, in 40 vaginal candidiasis patients. The patients were randomly divided into two groups: (1) Treated with suppositoires containing propolis wax from *Tetragonula* sp. (5%) and Oleum Cacao (n = 20) and (2) treated with the standard antifungal agent, nystatin vaginal tablet (n = 20); administered one at night before sleep for seven days. The results showed that Propolis can improve the immune response against *C. albicans* by inhibiting the biofilm production and increasing the microbial activity of neutrophils [46], [47]. Other used potential anti-fungal compounds are essential oils, including thymol (found primarily in thyme and oregano) [48], and curcumin [49], that perform a cleansing, refreshing and lenitive action, promoting the tissue repairing and the cellular microenvironment recovery by acting as mucosal protection elements.

Another potentially useful natural mucopolysaccharide, is the hyaluronic acid (HA), a uniform, anionic, nonsulfated, linear glycosaminoglycan, composed of repeated disaccharide units that can reach high length and molecular weight [50]: It has been challenged into the vagina due to its moisturizing mucosal healing chemotactic and hydrating properties, significantly contributing to viscoelastic interstitial tissue replacement [51].

Our previous preclinical investigations demonstrated that the high molecular weight HA has antiviral, antibacterial and antifungal activity toward a few *Candida* species [52], [53], [54], [55], [56], [57]. Many clinical contributions confirm that hyaluronic acid gives remarkable adhesive, moisturizing, and repairing benefits in the vaginal mucosa [58], [59].

A total of 833 studies, reviewed by Campagnaro *et al.* [60], confirmed topical hyaluronic acid gel administration has vaginal estrogens-like effects, relieving the typical vaginal atrophy symptoms, including dryness, itching, and dyspareunia, in postmenopausal women. It improves the vaginal microenvironment allowing for a better migration and proliferation of mesenchymal and epithelial cells involved in tissue repair process and has a hydrating effect due to persistent adhesion to the mucosa, with recovery of cutaneous microlesions caused by friction due to vaginal dryness.

Local oxygen therapy, on the other hand, has a powerful regenerative, antibacterial and biostimulating effect; in fact, it increases the availability of oxygen to the tissues, promotes the tissue repair processes and enhances the synthesis through hydroxylation of its chains [61], [62], [63], [64]. It improves the oxygen-dependent transport of some antibiotics, such as tobramycin, across bacterial cell walls [65]. Specifically, this treatment can improve the damage

to the mucosae after gynecologic cancer radiotherapy, promoting neo-angiogenesis, enhancing high levels of vascular endothelial growth factor (VEGF) from macrophages and improving local hypoxia [66]. Especially, hyperbaric oxygen increases the VEGF and activates capillary endothelial cells to migration, forms tubules off-post-capillary venules, and connects to existing blood supplies [67], [68], [69]. The hyperbaric oxygen stimulates also induction of collagen synthesis, fibroblast proliferation, and antimicrobial defense [70].

Recent *in vitro* and *in vivo* studies have demonstrated that oxygen therapy is an antifungal weapon against *Aspergillosis* and *Zygomycosis* [71], [72]. It is supposed that the oxygen decreases acidosis of the inflamed areas, reducing the anaerobic metabolism improving the cell mediated reaction against the infection and phagocytosis [72].

By increasing the partial pressure of oxygen in ischemic tissues, anaerobic metabolism is reduced, and local pH may improve and promote the intracellular killing of fungi into neutrophils, monocytes and macrophages cytoplasm [72]. Gudewicz *et al.* observed the combined effect of oxygen and amphotericin B (antifungal medication) to inhibit the growth of *Candida albicans* [73]. Oxygen tensions of 1800 mm Hg for 90 min in the presence of amphotericin B showed an enhancement of both minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) [73]. Condemi *et al.*, in a pilot trial, showed that the concomitant administration of topical hyperbaric oxygen and hyaluronic acid can have therapeutic efficacy in the treatment of vulvar-vaginal atrophy in 25 post-menopausal women [74].

On the basis of this literature contribution, the aim of our anecdotal, retrospective, spontaneous trial has been to evaluate the efficacy of the association between high concentration oxygen and hyaluronic acid for treatment of relapsing candidiasis.

Materials and Methods

The clinical study was approved by the local institutional review board and conducted in accordance with the ethical standards of the Declaration of Helsinki.

Patients

Forty-five women (30.9 ± 4.4 years) with relapsing candidiasis, and complaining of dryness, dyspareunia, pain, vaginal itching, and burning; appealed to our Second Opinion Medical Consulting, from January 2019 to January 2020, and were included in the present protocol (Table 1). The Second Opinion Medical Network is a consultation

Table 1: Patient's demographic characteristics

Patient's characteristics	Value
Number of patients (women)	45
White race, n	45
Geographic region, Italy, n	45
Age, years	30.9 ± 4.4
Weight, kg	61.1 ± 7.8
BMI, kg/m ²	20.8 ± 2.3
Candidiasis, n	24
Candidiasis+cystitis, n	21
Disease duration, years	≥ 5

Data are presented as the mean \pm SD. BMI: Body mass index, SD: Standard deviation.

referral web and medical office system enclosing a wide panel of specialists, to whom any patient with any illness or syndrome not adequately satisfied with diagnosis or therapy can ask for an individual clinical audit [75], [76], [77], [78]. After signed the informed consent form, all the participants answered a life quality questionnaire describing the clinical symptoms, frequency of relapses and personal history.

Each participant has been also required to fill in before and after the treatment, the Vaginal Assessment Scale (VAS) and a modified version of the VAS, the vulvar assessment scale (VuAS), identifying the vulvar symptoms (dryness, itching, burning, and pain), and to undergo to a self-administered vaginal swab for microbiological analysis at baseline and at the end of therapy. The patients were instructed to insert the vaginal swab (Canestest[®] self-test for vaginal infections, Bayer S.p.A., Milan, Italy) 1–2-inches into the vagina, rotating the swab to collect sample on all sides of the tip, keep the swab in the vagina for 10 s, and then remove the swab and place it in a sterile tube. After 10 s, the patients check the tip swab to see if the color has stayed yellow or changed to blue-green (indicating vaginal infections). In addition, each woman self-tested the vaginal pH, always before and after the treatment, using a vaginal applicator (Gyno-Canestest[®] Vaginal Ph Self-test swab, Bayer S.p.A., Milan, Italy) that includes a pH indicator embedded into a biocompatible grip. It detects vaginal pH, providing information regarding vaginal infections such as VVC, vaginosis and trichomoniasis (Table 2).

Table 2: The initial self pH readings of patients before the treatment

Patients' initial self pH readings	Number of patients (before treatment)
6–7	21
7–8	24

The yellow indicator may turn in green/blue, if vaginal pH is a normal ($\text{pH} > 4.7$), denoting infections such as candidiasis or do not change color after 10 s, if vaginal pH is normal ($\text{pH}: 3.8\text{--}4.5$) [79], [80]. A standard vaginal examination to detect the elastic properties of pelvic floor tissues, elastography index (EI), was performed by a practicing gynecologist, at baseline and at the end of the last treatment section, using an transvaginal elastography, also known as elasticity imaging -EI-, (EPIQ7C Ultrasound System, Philips Medical Systems, Andover, MA, USA) consisting of C10–3v PureWave 10MHz vaginal probe [81], [82], [83]. It products 3-D tactile images based on generating a

stress in the tissues using various static or dynamic means and on measuring their consequent elastic properties by ultrasound or MRI [84], [85].

The VAS and VuAS are each 4-item questionnaires that determine the severity scale (range 0–3 points: 0 = none, 1 = mild, 2 = moderate, and 3 = severe) of dryness, soreness, irritation, and pain (dyspareunia or painfulness to touch with external stimulation) for both the vaginal and vulvar areas. In particular, the VuAS focuses on the external genitalia, including the tissue surrounding the vaginal opening, the labia minora, labia majora, clitoral hood, clitoris, and perineum. Lower scores indicate better health conditions [86].

Inclusion and exclusion criteria

The inclusion criteria were as follows: Diagnosis of VVC by, one or more than one molecular swab, such as microbiome-based polymerase chain reaction (PCR) assay, or by blood test, including IgA, IgM, and IgG antibodies test; clinical history of a least 6-year candidiasis relapses. The exclusion criteria were pregnant women, patients with sexually transmitted diseases, women that used hormone therapy (estrogens, progestins, and androgens) or vaginal hormone products (rings, creams, and gel) in the past 2 months before the enrollment.

The patients accepted to undergo oxygen/hyaluronic acid therapy treatment, once a week, for a total of 5 weeks at the outpatient clinic (Healthy Center, Sirio, Fidenza, Italy).

Detailed instructions about healthy hygienic and sexual behavior were given before and after the treatment: The patient should avoid intravaginal medications, vaginal douching, and sexual intercourse within 24 h of her clinical procedure and also then it.

The physicians of the Second Opinion Medical Consulting Network followed up weekly from remote (telemedicine), each treated patient as to state the effectiveness, tolerability, and side effects of the treatment, through WhatsApp and Skype or visit when required.

Treatment protocol

It included one/weekly session (total 5 sessions) with a specific device for gynecological practice (Caressflow[®], Caress Flow Srl, Bologna, Italy): A vaginal disposable cannula, connected to the machine body. Each patient is treated, inserting the vaginal cannula equipped with outlet holes, and releasing molecular oxygen at 1 Atm alone (for the first 10 min) and subsequently combined with sprayed 5 ml low molecular weight hyaluronic acid (for the next 5 min) (Figure 1). Post-treatment maintenance of one session per month was recommended. The intravaginal oxygen flow (95%

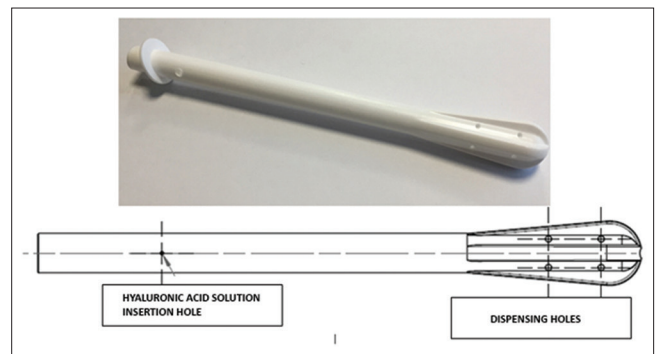


Figure 1: Vaginal disposable cannulas for injection of hyaluronic acid

pure oxygen delivered at a rate of 2 lt/min) has been chosen to optimize the best absorption by the vaginal mucosa. Highly concentrated oxygen spreads easily through the vaginal mucosa, counteracting the critical hypoxia of microcirculation impairment and recovering the superficial cells metabolism. After the oxygen session, hyaluronic acid solution (0.2% concentration, 10 ml) is sprayed through a special injection hole located in the upper part of the cannula (Figure 1). Due to its low molecular weight, is easily absorbed by the mucosa preconditioned with the pure oxygen flow. The low molecular weight hyaluronic acid penetrates easily in the mucosa prepared by the action of oxygen. All the patients were evaluated for the presence of candidiasis at the end of the last treatment session, with follow-up at 3 and 6 months from the end of treatment.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). The data were analyzed using an unpaired t-test with Welch's correction. $p < 0.05$ was considered significant.

Results

The Caress flow[®] protocol delivering HA and oxygen in the vagina of the women affected by candidiasis gave satisfactory results in terms of symptoms relieve and *Candida* disappearance at the end of the treatment. The mean VAS and VuAS scores measured at first visit were 2,660 and 2,622 and significantly ($p < 0.0001$) reduced to 1.311 and 0.77 at last visit (Figure 2). The measurements of the vaginal pH (value < 5) and of the vaginal swab (color yellow) after the last treatment session confirmed significantly ($p < 0.0001$) the absence of bacterial vaginosis, trichomonas vaginitis, or candidiasis (Figure 3).

Three months later in the follow-up, the percentage of patients who had only one VVC relapse was 4.44% (2/45), a percentage that increased just

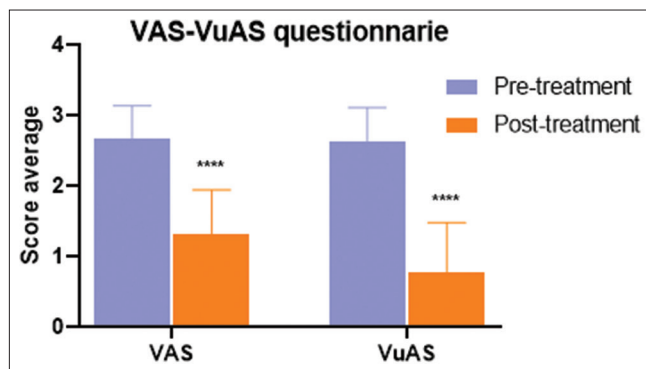


Figure 2: VAS and VuAS values pre- and post-treatment. There were significant differences. **** $p < 0.0001$ pre- vs. post-treatment

to 8,8% at six months (4/45). Figure 4 reported the relapsing events, for each patient, in the 6 months before treatment and in the 2 follow-up after treatment (3 and 6 month-follow up). The elastography index (EI) was significantly ($p < 0.0001$) increased after the last treatment session [mean \pm SD, 2.55 ± 0.545 (pre-treatment) vs. 4.48 ± 0.505 (post-treatment)] (Figure 5).

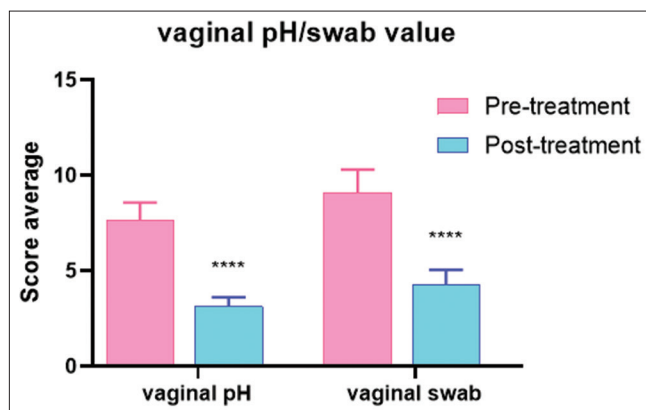


Figure 3: Vaginal pH and swab measurements before and post-treatment. There were significant differences. **** $p < 0.0001$ pre- versus post-treatment

The microbiological analysis of the secretions, in the 3 and 6-month follow-up, showed total elimination of fungal colonization in all the patients.

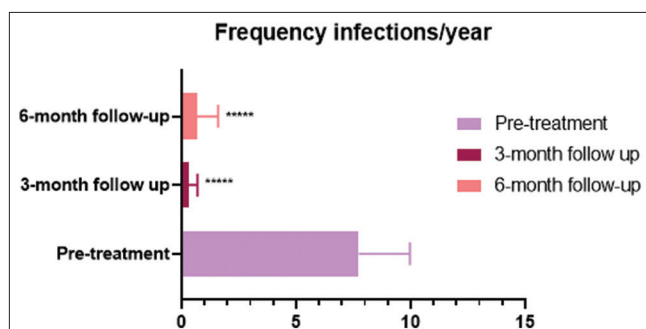


Figure 4: Frequency VVC infection/year pre-treatment and at 3 and 6-month follow-up. There were significant differences. **** $p < 0.0001$ pre- versus post-treatment

The tolerability was excellent: Indeed, no side effects of the treatment were reported by the patients that described the protocol “pleasant and refreshing.”

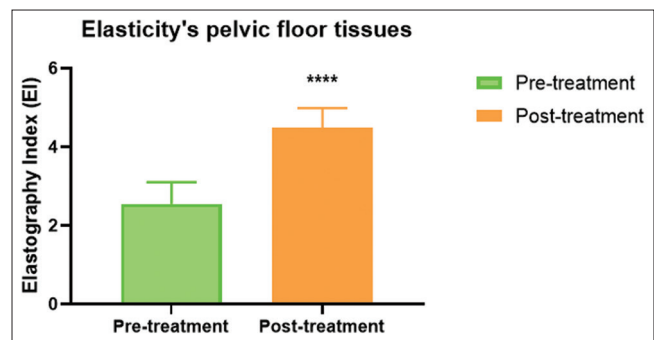


Figure 5: Elastography index (EI) values of pelvic floor tissues pre- and post-treatment. There were significant differences. **** $p < 0.0001$ pre- versus post-treatment

Combined oxygen therapy with hyaluronic acid has proved to be a valid method for treating the symptoms associated with relapsing candidiasis, capable of resolving both the acute phase of the infection and effectively preventing its reappearance. It is a totally painless therapy, with excellent compliance by patients.

Discussion

Our observation suggests that the Caressflow[®] protocol combining hyaluronic acid and oxygen has antimicrobial, antifungal, antioxidative, and also anti-inflammatory properties. Selectively the oxygen enhances the reparative processes of the inflamed mucosa and the collagen synthesis by the hydroxylation pathway and induces a neo-angiogenetic stimulation through the release of the vascular endothelial growth factor (VEGF) [74], [87], [88], [89]. The amount of oxygen up taken by plasma is 10–20 times higher than normal, and oxygen diffusion into tissues is strongly increased.

On the other side, hyaluronic acid, a natural polysaccharide, binds large amount of water molecules rehydrating, and re-structuring the inflammation-injured skin and mucous surfaces [90]. The safety and effectiveness of HA at different molecular weights in VVA patients have been stated by several studies [91], [92], [93].

As to the mechanisms of action, the low molecular weight hyaluronic acid spreads into the deeper vaginal layers [94], and can block the intercellular adhesion molecule (ICAM)-1 receptor, reducing inflammation and secretion of pro-inflammatory cytokines [95].

The individual interviews with the patients by mean of Skype or physician’s visit showed improvement in life quality, a notable goal especially for recurrent VVC, source of discomfort in the social daily life relationships, in the partner relationships and sexual intercourse. In fact, the life quality scores improved

progressively during the treatment in terms of intimacy and sexual intercourse fitness but also of mood and social behavior.

The main limitations of our study were (1) the small clinically cohort of patients and (2) the absence of a control group. Given the small size of the patient sample, we cannot exclude error rates (Type 1 and Type 2 errors) and cannot ensure that our results may be replicated in future research with larger sample size. However, this preliminary observation and the positive outcome are very promising and recommend a further major evidence based clinical trial. The identification of control group was also difficult because Caressflow[®] is a specific combination of gas and a natural mucopolysaccharide; in a possible next study a single- or double-blind placebo effect might be evaluated by a sham treatment with air flow and saline being our study just a basic reference of the procedure.

Conclusion

The combined oxygen therapy with hyaluronic acid gave definite symptomatic benefits in this cohort of relapsing candidiasis in the acute phase of the infection. The 6-month follow-up, also detected a lower reinfection rate compared with the historical available data. The procedure is totally painless with excellent compliance by patients and no untoward effects.

The Caressflow[®] device is non-invasive and repeatable treatment and can thus be considered a profitable hygienic procedure to be periodically repeated for optimal environmental conditions and functions of the vulvar-vaginal apparatus.

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