

ORIGINAL ARTICLE

Microablative fractional CO₂ laser improves dyspareunia related to vulvovaginal atrophy: a pilot study

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Objective: This pilot study aimed to assess the efficacy in treating sexually active menopausal patients who had dyspareunia related to vulvovaginal atrophy (VVA).

Materials and methods: The intensity of VVA symptoms was recorded for each patient. Patients were administered the Short Form 12 (SF-12) and the female sexual function index (FSFI) to assess quality of life and sexual function, respectively. An objective evaluation of female urogenital health was performed using the Gloria Bachman Vaginal Health Index (VHI).

Results: At 12-week follow-up, the laser treatment was efficacious in improving dyspareunia in 100% of patients included in the study ($n = 15$). The intensity of dyspareunia significantly decreased from baseline (8.7 ± 1.0) to 12-week follow-up (2.2 ± 1.0 ; $p < 0.001$). In addition, all other VVA symptoms significantly ameliorated at the same follow-up. Furthermore, after the treatment, a significant improvement in quality of life (QoL) and sexual function were shown.

Conclusions: This pilot study demonstrated that treatment with the microablative fractional CO₂ laser of patients with dyspareunia related to VVA was efficacious at 12-week follow-up.

Keywords: Dyspareunia, Fractional CO₂ laser, Menopause, Vaginal atrophy, Vaginal dryness

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INTRODUCTION

Vulvovaginal atrophy (VVA) is a physiological process resulting from the drop of estrogen that occurs in women during menopause (1). The vagina becomes narrower and shorter, and frequently the introitus can constrict. VVA is associated with a progressive loss of elasticity and of rugal folds of the vaginal lining which becomes thinner and may show petechiae. Sexual dysfunctions and absence of sexual activity are frequent conditions in patients with VVA symptoms. In fact, sebaceous glands reduce the production of secretions and therefore, during sexual intercourse, lubrication is decreased and delayed (2). The typical symptoms of VVA are vaginal burning and discharges, itching, dryness, irrita-

tion, dysuria and dyspareunia (3-5). In the 7 main studies of VVA to date, the prevalence of vulvovaginal symptoms was consistently about 50% (3, 6-10). VVA is a relevant issue in menopausal women and significantly deteriorates their quality of life (QoL) and sexual function (9-13).

The severity of symptoms and the efficacy and safety of treatment for each patient, as well as women's preference, influence the choice of therapy. First-line therapies recommended by the North American Menopause Society for symptomatic women with VVA include vaginal moisturizers, continued sexual activity, and lubricants which have the main goal to alleviate symptoms (14). When these therapies are not effective and satisfactory for patients, estrogen treatment should be considered in the absence of contraindications.

Although local estrogen therapies are effective (14, 15), the rate of medication adherence among patients is variable (52%-74%) (16). Furthermore, data on the long-term safety (more than 1 year) of these medications are lacking, and although local estrogen therapies do not seem to increase the risk of venous thromboembolism (VTE) (15), no information is available in high-risk patients (14). In addition, there are categories of patients (such as those with a history of breast cancer or endometrial cancer) in which the management depends on the woman's preference, needs, understanding of potential risks and consultation with the oncologist (14), but the use of estrogens is not properly indicated.

Fractional CO₂ laser has shown tissue remodeling properties in many body districts, such as the skin of the face, neck and chest, with the effect of producing new collagen and elastic fibres (17-20).

In fact, the generated supraphysiologic level of heat obtained with a CO₂ laser is able to induce a heat shock response, which can be defined as temporary changes in cellular metabolism. These changes are rapid and transient, and are characterized by the activation of a small family of proteins referred to as the heat shock proteins (HSP). HSP 70, which is overexpressed following laser irradiation, causes the stimulation of transforming growth factor- β (TGF- β), and it is known that TGF- β plays a crucial role in the inflammatory response and the fibrogenic process. In this process, the fibroblasts are the key cells, because they produce collagen and extracellular matrix. An *ex vivo* study on vaginal specimens collected during reconstructive pelvic surgery demonstrated connective tissue remodeling after treatment with a fractional CO₂ laser at predetermined parameters (21). Recently, a pilot study has shown the feasibility, efficacy and safety at 12-week follow-up of a fractional microablative CO₂ laser in the treatment of VVA (22).

Given this background, the present pilot study was designed to assess the efficacy of a fractional CO₂ laser in treating sexually active menopausal patients with dyspareunia related to VVA.

METHODS

Study design

This prospective pilot study was conducted between September and December 2012 and included postmeno-

pausal women with dyspareunia related to VVA. The study protocol was approved by the hospital research review committee. Women entered the study after an informed written consent was obtained.

Study population

Inclusion criteria for referral were being sexually active, with dyspareunia related to VVA, age >50 years, absence of menstruation for ≥ 12 months and not responding/being unsatisfied with previous local estrogen therapies. Exclusion criteria were use of any hormone replacement therapies (either systemic or local) within the 6 months prior to inclusion in the study; use of vaginal moisturizers, lubricants or any other local preparation within the 30 days prior to inclusion in the study; acute or recurrent urinary tract infections (UTIs); active genital infections (e.g., herpes genitalis, candida); prolapse staged $\geq II$ according to the pelvic organ prolapse quantification (POP-Q) system (23); previous reconstructive pelvic surgery; any serious disease or chronic condition that could interfere with study compliance; and psychiatric disorders precluding informed consent.

Study protocol

Postmenopausal women were treated intravaginally with the fractional microablative CO₂ laser system (SmartXide² V²LR, Monalisa Touch; DEKA, Florence, Italy), using the following settings: dot power 30 W, dwell time 1,000 μ s, dot spacing 1,000 μ m and the smart stack parameter from 1 to 3. After decreasing the dot power to 20 W, the vaginal introitus was initially treated, and laser energy was transmitted through a vaginal probe that was then slowly inserted and rotated along the vaginal canal, to provide a complete treatment of the vaginal wall. A treatment cycle included 3 laser applications. Time points of the study were at baseline (T1), at week 4 (T2), at week 8 (T3) and at week 12 (after 4 weeks from the last laser application, T4). The procedure was performed in the outpatient clinic and did not require any specific preparation (e.g., analgesia/anaesthesia).

Data collection

Sociodemographic characteristics of the study sample were collected at baseline (T1) and inclusion/exclusion

criteria were verified before starting the first laser application. At each time point of the study (T2, T3, T4), women were evaluated by using the vaginal health score index (VHIS) which consists of 5 measures: elasticity, fluid volume, pH, epithelial integrity and moisture. Each parameter is graded from 1 to 5. If the total score is <15, the vagina is considered atrophic (24). The severity of VVA symptoms (vaginal burning, vaginal itching, vaginal dryness, dyspareunia and dysuria) was measured using a 10-cm visual analog scale (VAS), where the left extreme of the scale indicated “absence of symptom” and the right indicated “symptom as bad as it could be.” The intensity of VVA symptoms was evaluated before starting the first laser application (T1) and at T2, T3 and T4. At T1 and at T4, postmenopausal women completed the Italian version of the Short Form 12 (SF-12) to assess physical (PCS12) and mental (MCS12) component summary scores of QoL (25) and the Italian version of the Female Sexual Function Index (FSFI) (26, 27).

As previously described, a FSFI full scale score of 26.55 has been demonstrated to be a good cutoff score to distinguish women with or without sexual dysfunction (28).

At 12-week follow-up (T4), the women rated the overall degree of satisfaction with the treatment by answering the following question: “Taking into consideration the variations in VVA symptoms, in overall well-being and QoL, as well as the adverse effects experienced, if any, how would you define your level of satisfaction with the laser treatment?” Answers were scored on a 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied). Satisfaction with the treatment was defined when the answers were “very satisfied” or “satisfied.” According to the intention-to-treat analysis, those women unable to tolerate the insertion of the probe due to the degree of VVA and/or vaginal stenosis would be considered as “very dissatisfied.”

The primary outcome of the study was to evaluate the change in the intensity of dyspareunia between baseline and 12-week follow-up. Secondary outcomes of the study were the evaluation of QoL, sexual function and patients’ satisfaction with the laser procedure.

Statistical analysis

Data presented in the text and tables are reported as means \pm standard deviation, medians or percentages (%).

TABLE I - BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Age, mean \pm SD	57.3 \pm 3.0
BMI, mean \pm SD	23.1 \pm 1.2
Smokers, no. (%)	6 (40.0)
Level of education, no. (%)	
Primary	1 (6.7)
Secondary	10 (66.6)
University	4 (26.7)
Patients with previous live births, no. (%)	14 (93.3)
Parity, median (range)	1 (1-3)
Sexual active patients, no. (%)	15 (100)
Previous hormone replacement therapy, no. (%)	5 (33.3)
Time of hormone replacement therapy, median months (range)	18 (2-26)

The normal distribution of continuous variable data was evaluated with the Kolmogorov-Smirnov test. Continuous variables were analyzed using the paired *t*-test and the Wilcoxon signed rank test accordingly to data distribution. Data were analyzed using SPSS software, version 21.0 (SPSS Science, Chicago, IL, USA).

RESULTS

Fifteen patients were invited to participate in this pilot study, and all agreed (100%). The baseline characteristics of the study population are listed in Table I. All patients enrolled in the study underwent an entire cycle of treatment (3 laser applications) and completed the 12-month follow-up (T4).

Dyspareunia (primary outcome) and sexual function (FSFI)

All patients included in the study were sexually active and reported dyspareunia due to VVA at baseline. The mean intensity of dyspareunia significantly improved between baseline (8.7 \pm 1.0), T2, T3 and T4 ($p < 0.001$ for all comparisons; Tab. II).

The mean FSFI score (\pm SD) at baseline was 12.2 \pm 1.0. The mean FSFI significantly ameliorated at T4 (27.3 \pm 0.9;

TABLE II - VHI SCORES, PREVALENCE AND INTENSITY OF SYMPTOMS RELATED TO VULVOVAGINAL ATROPHY DURING THE STUDY

	Baseline (T1) (First laser)	4-week follow-up (T2) (Second laser)	8-week follow-up (T3) (Third laser)	12-week follow-up (T4)
VHI (mean ± SD)	12.9 ± 3.0	17.8 ± 2.0*	19.0 ± 2.2*†	22.1 ± 2.3*†‡
Dyspareunia [§] (no., mean ± SD)	8.7 ± 1.0 (n = 15)	3.5 ± 0.8* (n = 15)	2.1 ± 1.0*† (n = 15)	2.2 ± 1.0*† (n = 15)
Vaginal dryness [§] (no., mean ± SD)	7.2 ± 1.1 (n = 13)	2.8 ± 0.7* (n = 13)	1.5 ± 1.1*† (n = 13)	1.7 ± 0.9*† (n = 13)
Vaginal burning [§] (no., mean ± SD)	6.9 ± 2.7 (n = 13)	2.5 ± 0.9* (n = 13)	1.9 ± 2.3*† (n = 13)	1.5 ± 1.9*† (n = 13)
Vaginal itching [§] (no., mean ± SD)	5.6 ± 1.3 (n = 11)	2.5 ± 0.9* (n = 11)	1.8 ± 0.8* (n = 11)	1.6 ± 0.7*† (n = 11)
Dysuria [§] (no., mean ± SD)	5.1 ± 0.9 (n = 9)	2.9 ± 0.7* (n = 9)	1.6 ± 0.8*† (n = 9)	0.8 ± 1.0*† (n = 9)

Data are presented as means ± standard deviation.
 VAS = visual analog scale; VHI = vaginal health score index.
 *Statistical significant difference with T1.
 †Statistical significant difference with T2.
 ‡Statistical significant difference with T3.
 §Measured on a 10-cm VAS scale (range: 0-10).

TABLE III - FSFI TOTAL AND DOMAIN SCORES

	Baseline (T1) (First laser)	12-week follow-up (T4)
Desire	2.2 ± 0.7	3.4 ± 0.7*
Arousal	2.2 ± 0.4	4.1 ± 0.4*
Lubrication	1.4 ± 0.2	4.4 ± 0.6*
Orgasm	2.4 ± 0.7	4.9 ± 0.8*
Satisfaction	2.5 ± 0.5	5.0 ± 0.3*
Pain	1.5 ± 0.2	5.5 ± 1.1*
Total score	12.2 ± 1.0	27.3 ± 0.9*

Data are presented as means ± standard deviation.
 FSFI = female sexual function index.
 *Statistical significant difference with T1.

p<0.001; Tab. III). A significant improvement was reported between baseline and T4 in all FSFI domains (p<0.001 for all comparisons; Tab. III).

Changes in vaginal health index, in other VVA symptoms and QoL (SF-12)

The mean score for the VHI at baseline was 12.9 ± 3.0. After the first laser application, the results for VHI improved significantly (p<0.001). A significant amelioration, compared with baseline, was also observed at T2, T3 and

TABLE IV - QUALITY OF LIFE (SF-12) SCORES

	Baseline (T1) (First laser)	12-week follow-up (T4)	p Value
PCS12	43.8 ± 10.9	55.7 ± 0.3	<0.001
MCS12	41.9 ± 11.7	50.7 ± 1.1	0.048

Data are presented as means ± standard deviation.
 PCS12 = physical component summary; MCS12 = mental component summary.

T4 (p<0.001 for all comparisons). Table II summarizes the results for VHI and the comparison between the VHI scores at each time.

At baseline, 13 women (86.7%) reported vaginal dryness and burning, 11 (73.3%) had itching and 9 (60.0%) had dysuria. When compared with baseline, all VVA symptoms significantly improved at T4 (p<0.05 for all comparisons). Table II summarizes the severity of pain symptoms and the comparison between their severity scores at each time.

Finally, both PCS12 and MCS12 scores significantly improved at T4 when compared with baseline (Tab. IV).

Patient's satisfaction with the laser procedure at 12 weeks

At 12-week follow-up, 6 women (40.0%) were very satisfied and 9 (60.0%) were satisfied with the laser procedure.

No patient was uncertain, dissatisfied or very dissatisfied with the laser treatment at 12-week follow-up.

Characteristics of the laser procedure

The mean (\pm SD) time required for the laser application was 5.1 ± 1.2 minutes at the first application. A trend for a decrease in the time required to complete the procedure was observed at the second application (4.2 ± 1.0 ; $p = 0.063$) and a significant reduction was reported at the third application (3.9 ± 0.5 ; $p = 0.008$). No adverse event related to the laser procedure was recorded.

DISCUSSION

Women's life expectancy in Western countries is around 80 years, and it is still rising. In the United States more than 50 million women were 50 years old or older in 2010 (29). Considering the average age of menopause in this population (50.5 years) (30) and the increasing life expectancy, most of these women will live around 40% of their lives after menopause. Therefore, health in menopausal women has become a primary aim for every health care system in these countries (31). Menopause has been considered for many years as a disease due to estrogen insufficiency, which could be managed by hormonal treatment (HT). However, in 2002, the results of the Women's Health Initiative trial shed a new light on this kind of treatment and led to a reconsideration of the benefit-to-risk ratio of HT (32). Furthermore, after 2002, the evolution of HT initiation among newly postmenopausal women after the release of this trial changed significantly. In fact, the age-standardized rate of HT initiation (no more than 1 year after menopause onset) in newly postmenopausal women decreased by 69.9% (33). Taking into consideration this background, the development of new nonhormonal strategies for the successful and safe treatment of menopause-related symptoms should be encouraged and aimed for.

VVA is a relevant concern for women of menopausal age, and different investigations have demonstrated that this problem consistently deteriorates QoL and the sexual health of women (7, 34-36).

A recent survey investigated how vaginal discomfort affects the normal life of menopausal women in the United States (36). Specifically, 80% of women investigated considered vaginal discomfort to negatively impact their lives, particu-

larly concerning sexual intimacy (75%), ability to have a loving relationship (33%) and overall QoL (25%); women also felt that it made them feel old (36%) and affected their self-esteem (26%) (36). Another survey conducted in the United States aimed to assess postmenopausal women's experience with VVA and perception of VVA symptoms (35). The most frequent VVA symptoms were dryness (55%), dyspareunia (44%) and irritation (37%). Eighty-five percent of partnered women referred to having lost some degree of intimacy with their partner, 59% indicated that VVA symptoms detracted from enjoyment of sex, 47% of partnered women indicated that VVA interfered with their relationship, 29% reported that VVA had a negative effect on their sleep and 27% reported that VVA had a negative effect on their general enjoyment of life (35). Although local estrogen therapies are effective in the improvement of VVA-related symptoms (14, 15), their use is not recommended in breast cancer or endometrial cancer patients, and more research should better define their long-term safety.

This pilot study investigated, for the first time, the efficacy of a fractional microablative CO₂ laser in treating sexually active menopausal patients with dyspareunia related to VVA. Furthermore, the laser procedure was safe, and no adverse event was recorded, although this finding should be interpreted with caution due to the small number of patients included in the study. At 12-week follow-up, the laser treatment was demonstrated to be efficacious in improving dyspareunia in the 100% of patients included in the study. In addition, there was a significant amelioration of sexual function, as confirmed by the improvement in all FSFI domains. Interestingly, all VVA symptoms had already significantly ameliorated after the first laser application, and a further significant improvement was reported at 12-week follow-up. Evaluation of the VHI results demonstrated a significant improvement between baseline and the end of treatment. Furthermore, there was a significant improvement in the SF-12 (both the MCS and PCS scores).

The major limitation of this study was its small sample size. However, this was a pilot study to investigate the efficacy of the laser procedure. A strength of this study was that the clinical benefit was achieved in a population of patients refractory to local estrogen therapy, who therefore may be considered to be more difficult manage.

Further, larger studies are awaited to confirm these preliminary results and to evaluate the long-term efficacy of the laser treatment. Furthermore, randomized trials comparing the laser procedure versus systemic/local hormonal

treatments are needed to assess the outcomes and the costs of the 2 therapies. In addition, future research should investigate the potential role of microablative CO₂ laser for the treatment of VVA in other categories of women such as oncological patients after radiotherapy and/or chemotherapy treatment and younger patients with premature ovarian failure.

In conclusion, this pilot study demonstrated, for the first time, that treatment with a microablative CO₂ laser of patients with VVA symptoms is efficacious in treating patients with VVA symptoms, in particular dyspareunia. The findings of this investigation, if confirmed by larger studies, may give the opportunity for a safe and effective treatment in women who are normally contraindicated to receive estrogen therapy.

Disclosures

The study was in adherence with the Declaration of Helsinki.

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Conflict of Interest: Dr. Stefano Salvatore has had financial relationships (lectures, member of advisory boards and/or consultant) with Pfizer Inc and Astellas. The other authors did not report any potential conflicts of interest.

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