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Is vaginal fractional CO_2 Laser treatment effective in improving overactive bladder symptoms in post-menopausal patients? Preliminary results

A. PERINO[1], G. CUCINELLA[2], G. GUGLIOTTA[3], S. SAITTA[4], S. POLITO[5], B. ADILE[2], R. MARCI[5], G. CALAGNA[1]

[1]Department of Obstetrics and Gynaecology, University Hospital, Palermo, Italy;
[2]Urogynecology Unit, 'Villa Sofia-Cervello' Hospital, Palermo, Italy;
[3]Department of Human Pathology, School and Division of Allergy and Clinical Immunology, University of Messina, Messina, Italy;
[4]Department of Obstetrics and Gynaecology, "Barone I. Romeo" Hospital, Patti (Messina), Italy;
[5]Department of Morphology Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy.

Abstract. – OBJECTIVE: To evaluate the role of vaginal fractional CO_2 laser treatment in the relief of Overactive Bladder (OAB) symptoms in post-menopausal women.

PATIENTS AND METHODS: Post-menopausal women who complained of one or more symptoms related to vulvo-vaginal atrophy (VVA), who experienced symptoms of OAB and who underwent vaginal treatment with fractional CO_2 laser were enrolled in the study. At baseline (T0) and 30 days post-treatment T1), vaginal status (using Vaginal Health Index – VHI), subjective intensity of VVA symptoms (using a visual analog scale – VAS) and micturition diary were evaluated. OAB symptoms were also assessed using a validated questionnaire.

RESULTS: Thirty patients were enrolled. A statistically significant improvement in VVA symptoms was observed and in VHI at T1 ($p < 0.0001$). A significant improvement was also identified in the micturition diary, in number of urge episodes and OAB-q ($p < 0.0001$). Nine of the 30 patients suffered from incontinence episodes, and had improved at T1.

CONCLUSIONS: In our experience, fractionated CO2 laser vaginal treatment has proved to be effective in improving OAB symptoms in post-menopausal women. Moreover, it is a safe and efficacious measure for the relief of VVA related conditions. Further long-term studies are needed to confirm these preliminary results.

Key Words:
CO_2 laser, Overactive bladder, Menopause, Vulvo-vaginal atrophy.

Introduction

Vulvo-vaginal atrophy (VVA) is defined as the progressive involution of urogynecological mucous membranes and tissues due to the menopausal drop in oestrogen levels[1,2]. It may lead to the occurrence of bothersome symptoms (vaginal dryness, itching, burning, irritation and dyspareunia), with a significant impact on quality of life (QoL) and sexual function[3,4].

Resolving "vulvo-vaginal aging symptoms" is a very timely issue, firstly because, considering the progressive aging of the general population, women may complain of these symptoms for more than one-third of their lives[5]. Many hormonal and non-hormonal strategies have been proposed to alleviate VVA symptoms[5-8], with the aim of identifying an effective, safe and long-term therapeutic option. Recently, by applying the principles of regenerative and anti-aging medicine, the use of fractional CO_2 laser has been extended to treating patients with VVA symptoms[9,10].

Through the topical remodeling of connective tissue and the production of new collagen, elastic fibers and other components of the extracellular matrix, laser CO_2 effects appear to overcome the negative vaginal changes related to climacteric estrogenic fall, with significant relief of related symptoms[9,10].

Data from our recent study indicate a significant improvement in VVA symptoms ($p<0.0001$) in women who underwent 3 sessions of fractional CO_2 laser vaginal treatment, with a relevant increase in vaginal health index (VHI) scores ($p<0.0001$) and a good level of satisfaction for the procedure[11]. During data collection for this study, an unexpected event occurred. A sample of menopausal women who had complained of urinary

Corresponding Author: Gloria Calagna, MD; e-mail: gloria.calagna83@gmail.com

problems, such as urgency or frequency, (in addition to VVA symptoms), reported a concomitant relevant improvement in urinary symptoms, after CO_2 laser treatment.

Starting from these clinical observations, we decide to evaluate the possible role of fractional CO_2 laser vaginal treatment in the relief of over active bladder (OAB) symptoms in post-menopausal women. Moreover, VVA symptom and VHI score improvements were also analyzed in the same study population.

Patients and Methods

Study Patients

The enrolled patients for this prospective observational pilot study were menopausal women who had complained of one or more symptoms related to VVA, who experienced symptoms of OAB and who underwent vaginal treatment with fractional CO_2 laser from January 2014 to January 2015. The inclusion criteria consisted of menopausal status (including early forms), one or more vulvovaginal symptoms (e.g., itching, burning, reduced lubrication, superficial and/or severe dyspareunia), non-response to previous oestrogen or local therapies, and diagnosis of OAB syndrome.

We defined OAB syndrome as all the cases which in woman complained for ≥3 months frequency of micturition on average ≥8 times per 24 h and at least three episodes of urgency (grade 3 or 4), with or without incontinence, during a 3-day micturition diary period at baseline[12].

Exclusion criteria at study entry were considered: clinically significant bladder outflow obstruction, significant post-void residual (PVR) volume (>200 ml), associated stress urinary incontinence (SUI), diabetic neuropathy, use of concomitant urinary incontinence medications, symptomatic urinary tract infection, active genital infections, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs, pelvic organ prolapse (POP) stage >II (according to the *Half Way System* for the quantification of POP)[13] and/or the use of HRT (systemic or local) up to 6 months before the study recruitment period.

Patients who used vaginal lubricants or any other local preparations were asked to suspend the application of these treatments and were included in the study after 30 days. Women who were using psychotropic drugs were excluded.

The study was approved by the Hospital Research Committee. All patients who were recruited for the study signed an informed consent form.

Laser Device

A fractional CO_2 laser system (SmartXide^2 V^{2}LR, Deka m.e.l.a., Florence, Italy) was equipped with a Vulvovaginal Laser Reshaping (V2LR) scanning system and appropriate probes for the vaginal area. This treatment modality is based on the interaction between a specific CO_2 pulsed laser and the vaginal mucosa.

A laser beam is emitted fractionally, and the CO_2 laser is focused in small spots (called DOTs) that are separated by healthy tissue. The laser beam penetrates the tissue and releases heat only when the set depth is reached. With software control and a radiofrequency system that feeds the laser source, it is possible to select the D-Pulse mode, the depth (SmartStak parameter, from 1-3) and the quantity (power, dwell time and spacing) of heat to be transferred to the tissue. The SmartStak function allows for the careful control of the vaporization depth and thermal action. Successive pulses are emitted in the same area for a Stack variable of 1-3 (in the vaginal application).

Every pulse is composed of a constant high-energy peak power to produce rapid ablation of the epithelial component of the atrophic mucosa, followed by longer emission times (dwell time) that allow the CO_2 laser to penetrate further into the mucosa. The pulses are distributed over the vaginal wall and are spaced (DOT spacing) to cover the entire treatment area. A specific probe is used to deliver the pulses, which allows for energy emission at 360°.

In this study, a calibrated probe was specifically utilized for vaginal application, easily inserted into the vaginal canal. The laser is projected towards a 45°-oriented mirror that is placed at the tip of the probe to be reflected on the vaginal walls but not the uterine cervix. To completely treat the vaginal area, it is necessary to emit many laser spots while progressively extracting the probe from the vaginal fundus up to introitus.

Each treatment spot consists of two passages: after the first energy release, the probe is rotated approximately 2 cm (using the regulatory tool) clockwise while remaining at the same vaginal distance.

Laser Treatment

Each patient was treated with the fractional CO_2 laser system using the vaginal probe. All patients underwent a complete cycle of three treat-

ment sessions that were spaced over a period of at least 30 days.

For each patient, a Pap test and vaginal swabbing were performed to rule out local lesions or infections. The procedure was performed in the outpatient clinic by two operators (A.P. and G.C.), and the patients did not receive analgesia or anaesthesia. The settings for intra-vaginal treatment were a *DOT power* of 40 watts, a *dwell time* of 1,000 µs, D*OT spacing* of 1,000 µm, *SmartStak* 2 and the *D-Pulse* mode; when necessary, the *DOT power* was reduced to 30 or 20 watts for the treatment of the vaginal introitus, which is a highly sensitive area (Figure 1).

As previously reported[11], before all treatment sessions, we proceeded to positioning of the speculum and observation of the vagina using colposcopic vision (Vaginal Health Index – VHI scoring was performed during this phase).

No local therapy was recommended after the laser sessions. To avoid vaginal irritation during the healing process, patients were advised to avoid coital activity at least for a week following each laser application. Any secondary or collateral effects of the treatment were recorded. For study analysis, two relevant time points were considered for the evaluation of treatment results: baseline (T0) and 30 days after the last laser application (T1).

Study Data

Relevant demographic characteristics, pre-treatment clinical data and inclusion/exclusion criteria were recorded at T0. At T0 and T1, the vaginal status of the patients was evaluated using VHI score (obtained using colposcopic vision), which consisted of the following 5 parameters: elasticity, fluid volume, pH, epithelial integrity and moisture. Each parameter was graded from 1 (worst condition) to 5 (best condition).

Intensity of VVA symptoms was also evaluated at T0 and T1 (vaginal itching, vaginal burning, vaginal dryness and dyspareunia) using a visual analog scale (VAS), which is based on a score from 1 to 10, where 1 indicates the absence of symptoms and 10 indicates severe symptoms ("as bad as it could be").

At T0 and T1, eligible patients adduced a micturition diary, which was to be completed during the 3 days preceding the visit. In the diary, patients were asked to specify the number of micturitions, number of urgency episodes and number of incontinence episodes, for every considered day.

Moreover, patients rated the degree of associated urgency on the five-point Patient's Perception of Intensity of Urgency Scale (0, no urgency; 1, mild urgency; 2, moderate urgency; 3, severe urgency; and 4, urge incontinence)[12], and only cases

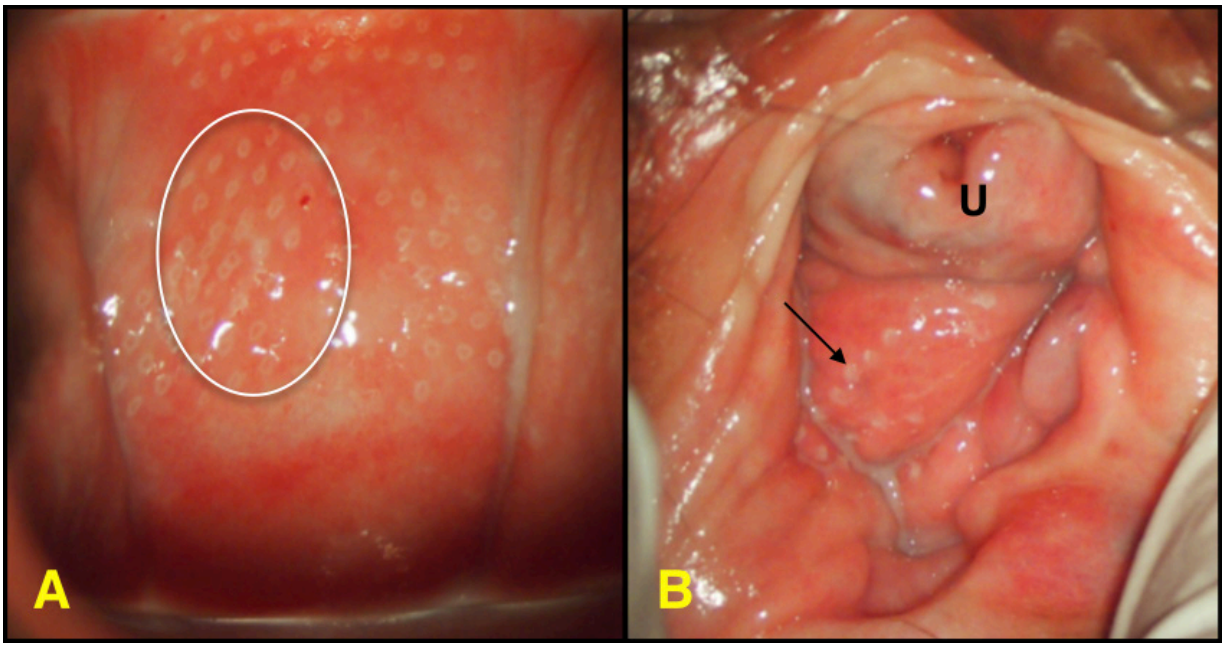

Figure 1. ***(A-B)*** Colposcopic view of vaginal walls immediately after a session of fractional CO_2 laser therapy. In ***A*** e ***B***, macropores of thermal ablation zones are highlighted in anterior vaginal wall (withe ring) and sub-urethral area *(arrow)*; U: urethral meatus.

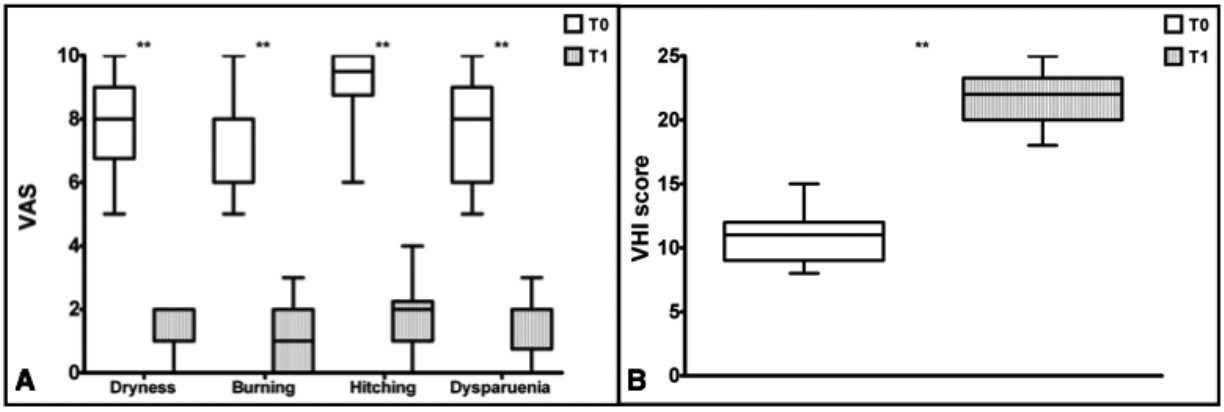

Figure 2. ***(A-B).*** VAS – dryness, – burning, – itching, – dyspareunia ***(A)*** and VHI score ***(B)*** are represented by Box-whiskers (medians, 1st and 3rd quartiles, minimum and maximum values). Statistical analysis was performed using Wilcoxon test, **means $p<0.0001$.

of 3 and 4 degrees of intensity were considered for analysis.

Overactive bladder symptoms were assessed using the validated Overactive Bladder Questionnaire Short Form (OAB-Q SF)[14].

Eventual adverse events which occurred or were referred by patients (during, immediately after treatment sessions, and until the end of study) were recorded. We considered any disorder, discomfort or injury, both local and general, arising in relation to the application of the vaginal fractional CO_2 laser as an adverse event.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows (version 17.0, SPSS Inc., Chicago, IL, USA). Data were presented as median/IQR. Differences between VAS at T0 and T1 were analyzed with Wilcoxon test. Statistical significance was set at $p<0.05$.

Results

In the study period, 30 patients were enrolled. Demographic characteristics are reported in Table I. Patients had used systemic HRT and/or vaginal estriol with no benefit, before vaginal CO_2 laser treatment, in 20% and 36.7% of cases respectively. All patients included into the study completed the study-protocol and carried out the final evaluation at T1. We observed a statistically significant improvement in VAS parameters concerning dryness (8/3 *vs.* 2/1.25; $p<0.0001$), burning (8/2.25 *vs.* 1/1; $p<0.0001$), itching (8/2 *vs.* 1/2; $p<0.0001$) and dyspareunia (9.5/1.25 *vs.* 2/1.25; $p<0.0001$) (Figure 2A).

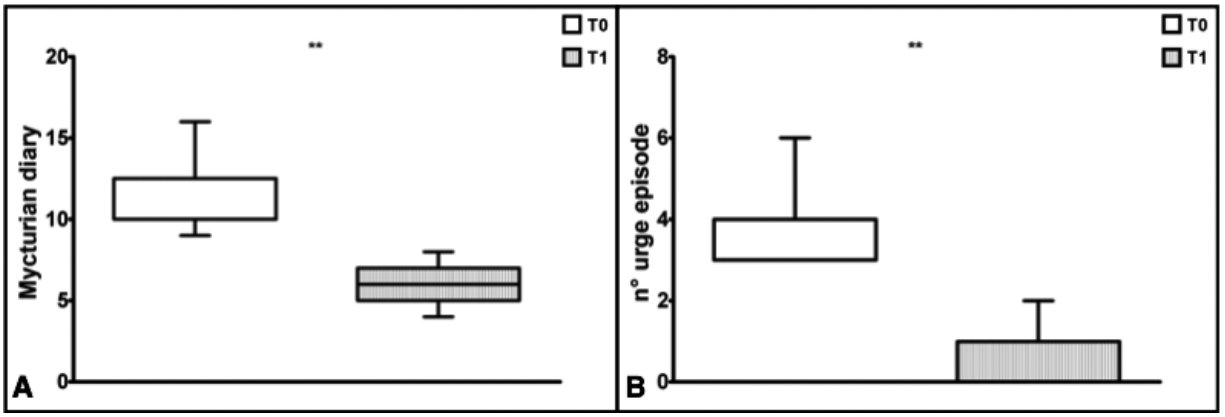

Figure 3. ***(A-B)*** Micturition diary ***(A)*** and n° urge episodes ***(B)*** are represented by Box-whiskers (medians, 1st and 3rd quartiles, minimum and maximum values). Statistical analysis was performed using Wilcoxon test, **means $p<0.0001$.

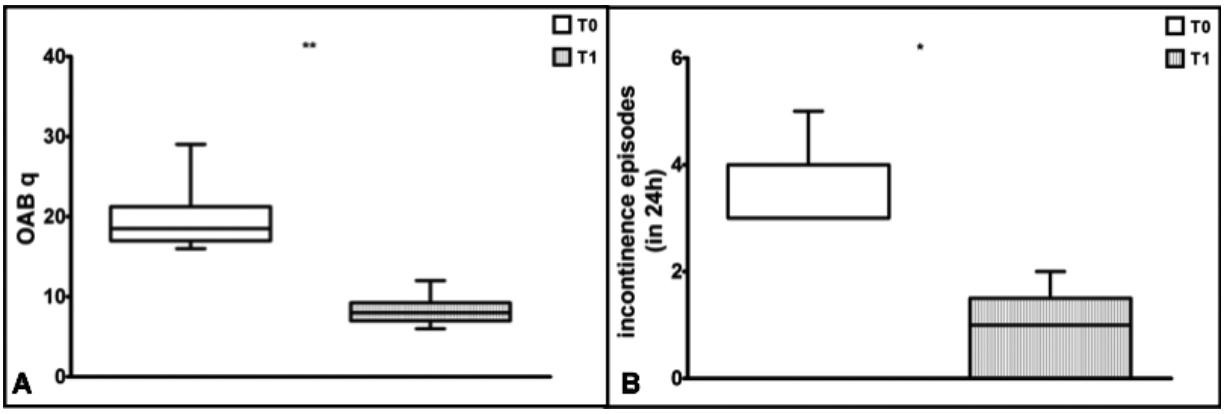

Figure 4. ***(A-B)*** OAB q ***(A)*** is represented by Box-whiskers (medians, 1st and 3rd quartiles, minimum and maximum values). Statistical analysis was performed using Wilcoxon test, **means $p<0.0001$. In ***B***, incontinence episodes (in 24h) are represented by Box-whiskers (medians, 1st and 3rd quartiles, minimum and maximum values); statistical analysis was performed using Wilcoxon test, *means $p<0.05$.

We also reported a significant improvement in VHI at T1 (11/3 *vs.* 22/3.25; $p<0.0001$) (Figure 2B), in micturition diary (10/2.5 *vs.* 6/2; $p<0.0001$) (Figure 3A), in number urge episodes (3/1 *vs.* 0/1; $p<0.0001$) (Figure 3B) and in OAB-q (18.5/4.25 *vs.* 8/2.25; $p<0.0001$) (Figure 4A). Nine of the 30 patients suffered from incontinence episodes, and had improved at T1 (3/1 *vs.* 1/1.5 episodes in 24 h; $p=0.006$) (Figure 4B).

No significant differences were observed between patients or between the sessions for the same patient. No adverse events due to fractional CO_2 laser treatment occurred. In no case was it necessary to stop the procedure because of patient pain or intolerance. No local therapies were prescribed to any patient after the sessions of laser treatment.

Discussion

Overactive bladder is a wide-spread problem characterized by symptoms of urinary urgency, frequency and nocturia, with/without urgency incontinence (UI) and in the absence of lower urinary tract infection[15,16]; it may cause significant disability, reduced QoL, along with social relationship and sexual function deterioration[17,18]. It is known that this chronic condition requires life-long therapy to control symptoms, with the aim of restoring QoL while balancing efficacy and side effects[19].

Generally, an early approach to the problem involves conservative measures such as dietary controls, fluid modification and pelvic floor muscle rehabilitation, but the results are frequently poor. Antimuscarinic agents are used as first-line pharmacotherapy in the management of OAB, with well-documented effectiveness in the clinical literature[18,20]. However, patients often discontinue this therapy for many reasons including intolerable side effects (dry mouth, constipation and blurred vision) or/and lack of sufficient symptom relief[21,22].

A recent pharmacological alternative is mirabegron, a β3-adrenoceptor agonist that elicits bladder relaxation during the storage phase of the micturition cycle, without inhibiting bladder voiding[23]. It provides treatment benefits in OAB patients and its tolerability profile suggests that it may represent a valuable therapeutic option[24,25]. However, randomized prospective trials are still lacking[23]. Likewise, with regard to intravesical botulinum toxin for management of OAB, a few controlled trial data exist on its benefits and safety[26]. Reported adverse events following botulinum toxin administration may be related to the drug (constipation, transitory asthenia, dry mouth) or the associated procedure (pain, haematuria)[26]; moreover, robust data are required on long-term outcomes and optimal dose of botulinum toxin.

Table I. Demographic characteristics of the study population.

Age (median/IQR)	56/8.5
Body Mass Index (median/IQR)	23.9/3.49
Parity (median/IQR)	1/1.25
Smokers (n, %)	5 (16.7)
Urge incontinence (n, %)	7 (23.3)
Previous HRT (n, %)	6 (20)
Previous vaginal estriol (n, %)	11 (36,7)
Other previous therapy (n, %)	21 (70)

Finally, neuromodulation therapy could be another possible approach[19]; in particular, sacral nerve stimulation with an implantable device has demonstrated the efficacy in managing OAB symptoms[27]. However, it has been limited in clinical practice due to several factors including invasiveness, associated costs, limitations in older adult patients and those who are frail or who have several medical comorbidities[28].

In this pilot study, we assessed the clinical effects of fractional CO_2 laser vaginal treatment on the main symptoms associated to OAB syndrome, such as frequency, urgency and eventual incontinence episodes, in a sample of post-menopausal women. Our results indicated a significant reduction of number of micturitions and number of urge episodes (p<0.0001) in women who underwent 3 sessions of vaginal CO_2 laser treatment. Concerning the subgroup of patients suffering from urge incontinence, a significant reduction in the number of daily episodes was shown (p<0.0001). Moreover, the changes of OAB-q score in T1 indicated a subjective significant improvement (p<0.0001), with particular reference to the incidence of OAB problems in QoL of the patients.

Finally, results of this study confirmed that CO_2 laser treatment was effective in improving VVA symptoms and VHI scores (p<0.001) at a T1 follow-up.

The observed phenomenon on OAB symptoms is explained starting from the anatomical characteristics of the urogenital tissue. It has been well demonstrated that urogenital organs are highly sensitive to the influence of oestrogen; oestrogen receptors have been found in the urethra and bladder trigone, as well as in the round ligaments and levator ani muscles[29]. As occurs in vaginal tissue, the progressive decline of estrogens during the climacteric produces atrophy of the urethral and bladder mucosa, causing urinary urgency, frequency and nocturia-OAB symptoms; accordingly, atrophy of muscles and reduction of collagen content may be important factors in the increased prevalence of urinary incontinence[30].

As previously reported[9], fractional CO_2 laser system can irradiate deeper layers of the vaginal wall and ultimately reactivate the extracellular matrix and collagen synthesis, with beneficial effects in the 3 layers of the vaginal wall (in contrast to estrogens or other local therapies that only treat the epithelium). In this way, it is possible to presume that the "regeneration" effect of the vaginal laser CO_2 treatment also involves the lower urinary tract (urethra and bladder), with a significant improvement of urogenital aging symptoms.

To the best of our knowledge, this is the first experience on the topic in international literature; however, this study has some limitations. First of all, the absence of randomization or a control group of patients; secondary, the small sample size considered and lack of long-term follow-up. Further studied are needed to confirm these results and to define the potentialities of this approach.

Based on these preliminary results, it would be advisable to perform a new study that includes a control arm (e.g. intravaginal estriol administration) to compare laser CO_2 with other proposed therapeutic options, in the contemporaneous relief of VVA and OAB symptoms, evaluating the long-term outcomes.

Conclusions

Our preliminary results suggest that fractionated CO_2 laser has a role in improving OAB symptoms in post-menopausal women. Moreover, achieved data confirmed that it is a safe and effective measure for the relief of VVA related problems. Considering the lack of a shared guideline for the management of OAB syndrome, we think that this study could lead the way to an alternative approach, tailored for menopausal women complaining of VVA and OAB symptoms.

Conflicts of interest

The authors declare no conflicts of interest.

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