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ORIGINAL ARTICLE

CO_2 laser and the genitourinary syndrome of menopause: a randomized sham-controlled trial

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ABSTRACT

Purpose: This study aimed to clarify the efficacy of intravaginal CO_2-laser treatment in postmenopausal women with genitourinary syndrome of menopause (GSM).

Materials and methods: This double-blind, randomized, sham-controlled trial included postmenopausal women diagnosed with GSM and bothersome dryness and dyspareunia. Treatment consisted of three sessions. Active CO_2-laser treatments (active group) were compared to sham treatments (sham group) with the primary endpoints being changes in dryness and dyspareunia intensity, as assessed by the 10-cm visual analog scale. Secondary endpoints were as follows: changes in Female Sexual Function Index (FSFI; total score and all domains), itching, burning, dysuria, and Urogenital Distress Inventory (UDI-6); incidence of symptoms; and presence of adverse events. All outcomes were evaluated at baseline and 4 months post baseline.

Results: Fifty-eight women (28 in the active group and 30 in the sham group) were eligible for inclusion. In the active group, dryness, dyspareunia, FSFI (total score), itching, burning, dysuria, and UDI-6 were significantly improved (mean [standard deviation] −5.6 [2.8], −6 [2.6], 12.3 [8.9], −2.9 [2.8], −2.3 [2.8], −0.9 [2.1], and −8.0 [15.3], respectively). In the sham group, dryness, itching, and burning were significantly improved (−1.9 [2], −1.4 [1.9], and −1 [1.9], respectively). All changes were in favor of the active group. After completion of the protocol, the proportion of participants with dryness, dyspareunia, and sexual dysfunction was significantly lower in the active group compared to those in the sham group (all $p < 0.005$).

Conclusions: CO_2 laser could be proposed as an effective alternative treatment for the management of GSM as it is superior to sham treatments.

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Introduction

Genitourinary syndrome of menopause (GSM) refers to clinical signs and symptoms related to anatomical and functional changes of urogenital tissues due to hormonal deficiency during menopause[1,2]. It comprises symptoms from the lower genital tract system (previously known as vulvovaginal atrophy [VVA] symptoms), sexual symptoms, and symptoms from the lower urinary tract system[1]. VVA symptoms (vaginal dryness, dyspareunia, burning, and itching) are the most common GSM symptoms; the cardinal symptom of VVA is the subjective dryness that is correlated to dyspareunia and other aspects of sexual dysfunction[2,3].

Management of GSM symptoms is personalized depending on the most bothersome symptom and may include a variety of approaches such as local/systemic, hormonal/non-hormonal, and combinatorial therapies[2,3]. Women's adherence and persistence to treatment are another essential factor for GSM treatment due to its chronic nature[2]. These elements of GSM management have led to the research of new therapeutic modalities, with the energy-based devices being increasingly used[4–9]. However, there is a lot of criticism regarding the lack of randomized controlled trials (RCTs) evaluating the safety and efficacy of energy-based devices addressing their possible placebo effect[5,6,9–14]. This has been stressed by regulatory bodies and has been debated among medical societies[10–14].

The aim of the current randomized, placebo-controlled trial is to evaluate the efficacy of the vaginal microablative fractional CO_2 laser in postmenopausal women with GSM diagnosis. Particularly, we evaluated whether active CO_2-laser treatment was potentially more successful than sham treatment in reducing bothersome GSM symptoms, comparing changes of dryness, dyspareunia, itching, burning, sexual functioning, urinary frequency (UF), and incontinence in postmenopausal women receiving three sessions (active or sham) of vaginally administered CO_2-laser treatments.

Methods

This study is a multicenter, randomized 1:1, placebo-controlled, double-blind trial which was conducted in two tertiary academic referral hospitals ('Alexandra' Hospital, Athens,

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Greece and San Rafaelle Hospital, Milan, Italy). The principles of the Declaration of Helsinki were followed, approvals from the local Ethics Committees were obtained, and all women signed informed consent forms. The trial has been registered with ClinicalTrials.gov (NCT03754205). The recommendations of the Consolidation Standards of Reporting Trials (CONSORT) statement were followed for the reporting of this trial.

Eligibility criteria involved postmenopausal women with GSM diagnosis according to the definition by the International Society for the Study of Women's Sexual Health and The North American Menopause Society, with no age limit[1]. Dryness and dyspareunia related to GSM had to be the two most bothersome symptoms in all women. Exclusion criteria were vulvodynia, vulvovaginitis (i.e. candidiasis at the time of selection), any vulvovaginal pathology, dryness, and dyspareunia induced due to reasons other than GSM (i.e. previous pelvic radiotherapy, Sjögren's Syndrome, etc.), prior treatment with intravaginal energy-based devices, use of non-hormonal/hormonal local therapies (3 and 6 months prior to the screening process, respectively), other pathologies that could interfere with participants' compliance to the protocol, pelvic organ prolapse > stage 2 according to the Pelvic Organ Prolapse Quantification (POP-Q) staging system[15], and a history of gynecological and/or breast cancer. Participants' eligibility was evaluated by experienced physicians who had no other involvement in the study protocol or the randomization–allocation process.

All laser treatments (active or sham) were performed using the microablative fractional CO_2 laser (SmartXide^2 V^{2}LR Monalisa Touch; DEKA, Florence, Italy) as previously described[16] by independent physicians (one at each center) unaware of the study protocol, who were not allowed to discuss or have any other involvement with the participants. The standard therapeutic protocol[16,17] of three therapies at monthly intervals was followed in both groups. Laser energy was released only in the active group. The power and the emission mode are the two parameters that define whether laser energy will be released. The parameters were as follows:

(1) Vaginal canal
- Active group: power, 30 W; dwell time, 1000 μs; spacing, 1000 μm; depth, SmartStak parameter 1–3 depending on treatment status; D-pulse mode; pulse energy, 43.2 mJ, 86.4 mJ, and 129.6 mJ at the first, second, and third session, respectively.
- Sham group: power, 0.5 W; dwell time, 1000 μs; spacing, 1000 μm; depth, SmartStak parameter 1; smart-pulse mode; pulse energy, 0 mJ at each session.

(2) Introitus and labial minora
- Active group: power, 24 W; dwell time, 400 μs; spacing, 1000 μm; depth, SmartStak parameter 1; D-pulse mode; fluence, 2.36 J/cm^2; pulse energy, 23.2 mJ.
- Sham group: power, 0.5 W; dwell time, 400 μs; spacing, 1000 μm; depth, SmartStak parameter 1; smart-pulse mode; fluence, 0 J/cm^2; pulse energy, 0 mJ.

The parameters were manually inserted by authorized nurses (one at each center) and remained hidden to the participants. They were the only responsible parties with access to the participants' allocation; no other implementation to the study's protocol or the participants was allowed. Participants could not guess in which group they were allocated, as they were naïve to intravaginal energy-based device treatment, were informed that the laser treatments might not produce any discomfort, the laser's screen was covered, and the sound of the laser was standard independent of the laser energy. In addition, participants were not allowed to use any moisturizers or lubricants or hormonal treatments until the end of the study protocol.

At baseline (before the initiation of the study protocol) and at 1 month following the third therapy (4 months), the intensity of dryness and dyspareunia, other aspects of sexual functioning such as orgasm, desire, arousal, and sexual satisfaction, as well as UF and incontinence were evaluated in all participants in both groups. Patient-reported outcomes (10-cm visual analog scale [VAS], Female Sexual Function Index [FSFI][18–20], and Urogenital Distress Inventory [UDI-6][21,22]) were used for these assessments. The VAS measures the level of symptoms intensity. Women were asked to draw a line between 0 ('no symptoms at all') and 10 ('symptoms as worse as possible') that corresponded to the level of symptom intensity. Incidence of dryness or dyspareunia was defined by responses >0. FSFI includes six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain domain) and a total score. A cut-off point of 26.55 for the total score distinguishes women with normal sexual function from those with sexual dysfunction[18]. Incidence of sexual dysfunction was defined by total FSFI score < 26.55. The UDI-6 may produce values from 0 to 100[23]; a higher score signifies more intense symptoms. All questionnaires were provided at baseline and 4-month follow-up by nurses (one at each site) unaware of the study protocol and with no other involvement with the participants and the study.

Primary endpoints were changes in dryness and dyspareunia intensity. Secondary endpoints were the following: changes in aspects of sexual functioning; changes in itching, burning, and dysuria intensity; changes in UDI-6; changes in dryness and dyspareunia incidence; changes in sexual dysfunction incidence; changes in UF, urge urinary incontinence (UUI), and stress urinary incontinence (SUI); and adverse events.

Statistical analysis

Participants were equally assigned by 1:1 block randomization to either active or sham treatment using the free online program Sealed Envelope (https://www.sealedenvelope.com/simple-randomiser/v1/lists). The block sizes were 4, 6, and 8. Allocation concealment was performed using the sealed opaque envelopes rationale. The envelopes were locked in a safe place with limited access for the aforementioned authorized nurse who had no other involvement in the study.

The G-power statistical program was used for the sample size calculation. The test family was the *F*-statistic. The type of power analysis was a priori and the methodology represents a design with two levels of the between-subject factor

of two study groups and two levels of the within-subjects factor of time. The effect size for this calculation used the ratio of the standard deviation of the effects for a particular factor or interaction and the standard deviation of within-subject effects. The power analysis was conducted for a single, two-group between-subjects factor, and a single within-subjects factor assessed over two time points. For this design, 27 participants per group achieves a power of 0.85 for the between-subjects main effect at an effect size of 0.36, a power of 0.95 for the within-subjects main effect at an effect size of 0.25, and a power of 0.95 for the interaction effect at an effect size of 0.25. With the assumption of a possible drop-out rate of 10%, the sample size increased to 30 cases per group.

Continuous variables (dryness, dyspareunia, FSFI, itching, burning, dysuria, and UDI-6) are presented as the mean and standard deviation. Qualitative variables are presented as absolute and relative frequencies. For the comparison of proportions, the chi-square test and Fisher's exact test were used. For the comparison of continuous variables between the sham and active groups, Student's *t*-test was utilized. Differences in changes of self-reported symptoms, FSFI, and UDI-6 scores during the follow-up period between the two study groups were evaluated using a general linear model of repeated-measurements analysis of variance. Scores that were not normally distributed were log-transformed for the analysis of variance. In a repeated-measure analysis of variance, three types of *p* values are presented: those that concern the comparisons among different time points, those that concern the comparisons between groups at each time point, and those that concern the interaction effect of time with the type of group in the study. All comparisons referred to mean differences and for this reason the effect size of the differences was used to calculate the sample size for a specific power and at significance level of 0.05. The correlation among the repeated measures was estimated at 0.5. Values of η^2 were computed in the repeated-measurements analysis as an effect size of the differences. An η^2 value more than 0.14 was considered large effect, between 0.14 and 0.06 intermediate effect, and less than 0.06 small effect[24]. All *p* values reported are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 23.0).

Results

Overall, 108 women were screened for eligibility. Finally, 60 of them qualified to be randomized. The CONSORT recommendations were followed for the identification process of participants as well as the flow of participants through the trial (Figure 1). Two participants in the active group dropped out of the study for personal reasons irrelevant to the study.

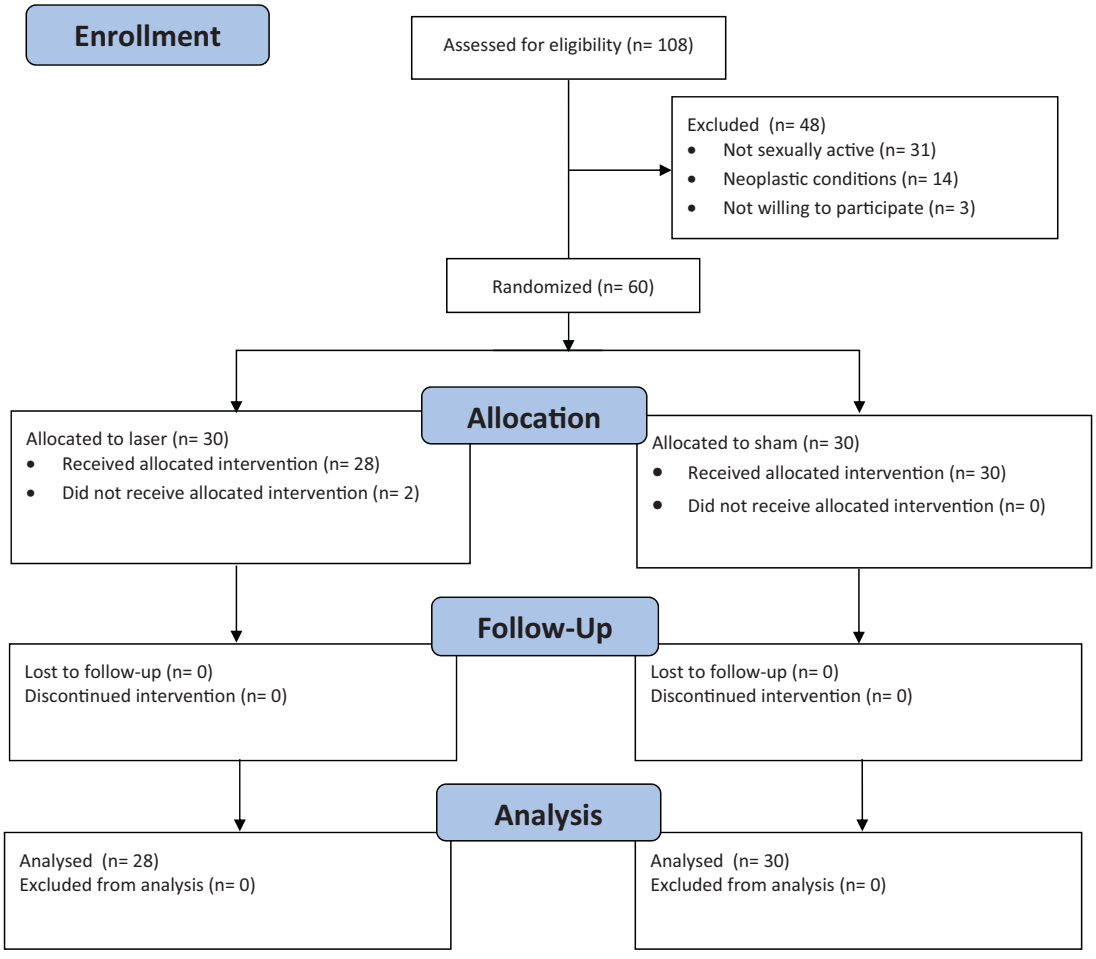

Figure 1. Identification process of participants.

Baseline characteristics (age 57.0 [6.9] vs. 58.4 [6.0] years, age at menopause 48.7 [4.9] vs. 49.7 [3.2] years, years since menopause 8.2 [4.9] vs. 8.7 [5.9], and all endpoints at baseline) were the same between the compared groups.

Primary endpoints

In the active group, dryness and dyspareunia were statistically significantly improved at 4 months compared to baseline with large effect size ($\eta^2 = 0.64$ and 0.72, respectively) (Table 1). In the sham group, dryness was statistically significantly improved with intermediate effect size ($\eta^2 = 0.12$), while dyspareunia was not (Table 1). In the between-groups comparison of changes, both dryness and dyspareunia were statistically significantly improved in favor of the active group (Table 1).

Secondary endpoints

In the active group, FSFI (total score and all domains), itching, burning, dysuria, and UDI-6 were statistically significantly improved with large effect sizes (all $\eta^2 \geq 0.14$) (Table 1). In the sham group, itching, burning, lubrication, and orgasm were statistically significantly improved with small or intermediate effect size (Table 1). All other continuous outcomes were not improved (Table 1). In the between-groups comparison of changes, all continuous outcomes except dysuria and UDI-6 were statistically significantly improved in favor of the active group (Table 1). Dysuria and UDI-6 improvement was the same between groups (Table 1).

The incidence of dryness, dyspareunia, sexual dysfunction, UF, UUI, and SUI in both groups is presented in Figure 2(a,b). At baseline, there were no differences between groups. At 4 months, the incidence of dryness, dyspareunia, and sexual dysfunction was lower in the active group compared to the sham group (57% [16/28] vs. 93% [28/30], $p = 0.002$; 67% [19/28] vs. 100% [30/30], $p < 0.001$; and 64% [18/28] vs. 97% [29/30], $p < 0.001$, respectively), while the incidence of UF, UUI, and SUI was the same between groups.

Serious adverse events were not reported by any of the participants in either group. A mild irritation of the vulva (that started during the procedure, lasted for about 30 min, and spontaneously resolved) was reported by all participants in the active group (28/28 [100%]) but not by participants in the sham group (0/30 [100%]).

Table 1. Changes of GSM symptoms.

Group	*Baseline, mean (SD)*	*4 months, mean (SD)*	*Change, mean (SD)*	p-*Value2*	η^2	p-*Value3*
Dryness						
Sham	7.5 (1.9)	5.6 (2.9)	−1.9 (2)	**0.006**	0.12	**<0.001**
Active	8.0 (1.7)	2.4 (2.9)	−5.6 (2.8)	**<0.001**	**0.64**	
p-Value1	0.327	**<0.001**				
Dyspareunia						
Sham	8.7 (1.4)	7.6 (1.9)	−1.1 (1.8)	0.176	0.03	**<0.001**
Active	8.6 (1.5)	2.6 (2.6)	−6 (2.6)	**<0.001**	**0.72**	
p-Value1	0.822	**<0.001**				
Itching						
Sham	3.1 (3.2)	1.8 (2.6)	−1.4 (1.9)	**0.004**	0.13	**0.015**
Active	3.9 (3.1)	1.0 (2.1)	−2.9 (2.8)	**<0.001**	**0.43**	
p-Value1	0.282	0.255				
Burning						
Sham	4.6 (3.4)	3.7 (3.4)	−1 (1.9)	**0.047**	0.07	**0.014**
Active	3.6 (3)	1.4 (2.4)	−2.3 (2.8)	**<0.001**	**0.35**	
p-Value1	0.440	**0.007**				
Dysuria						
Sham	0.9 (1.6)	0.6 (1.2)	−0.3 (1.5)	0.534	0.007	0.181
Active	1.6 (2.4)	0.6 (1.5)	−0.9 (2.1)	**0.016**	0.10	
p-Value1	0.343	0.793				
FSFI						
Total Score						
Sham	9.7 (7.8)	12.1 (8.3)	2.4 (4.9)	0.065	0.06	**0.001**
Active	11.4 (8.2)	23.8 (6.6)	12.3 (8.9)	**<0.001**	**0.60**	
p-Value1	0.416	**<0.001**				
Desire						
Sham	2.4 (1.1)	2.6 (1.3)	0.2 (1.3)	0.552	0.006	**0.001**
Active	2.1 (1.1)	3.2 (0.9)	1.1 (1.0)	**<0.001**	**0.34**	
p-Value1	0.173	**0.019**				
Arousal						
Sham	1.7 (1.9)	2.0 (1.8)	0.3 (1.0)	0.075	0.06	**0.002**
Active	1.8 (1.6)	3.6 (1.1)	1.8 (1.5)	**<0.001**	**0.41**	
p-Value1	0.490	**<0.001**				
Lubrication						
Sham	1.3 (1.6)	2.0 (1.7)	0.7 (1.2)	**0.022**	0.09	**0.005**
Active	1.8 (1.6)	4.3 (1.5)	2.5 (2.0)	**<0.001**	0.42	
p-Value1	0.216	**<0.001**				
Orgasm						
Sham	1.4 (1.8)	1.9 (1.8)	0.5 (1.0)	**0.023**	0.09	**0.008**
Active	1.7 (1.6)	3.7 (1.5)	2.0 (1.7)	**<0.001**	**0.40**	
p-Value1	0.323	**<0.001**				
Satisfaction						
Sham	1.8 (1.4)	2.1 (1.6)	0.3 (1.1)	0.217	0.03	**0.005**
Active	2.5 (1.5)	4.3 (1.2)	1.7 (1.7)	**<0.001**	**0.33**	
p-Value1	0.056	**<0.001**				
Pain						
Sham	1.0 (1.2)	1.5 (1.2)	0.4 (1.1)	0.070	0.06	**<0.001**
Active	1.4 (1.5)	4.5 (1.7)	3.1 (2.0)	**<0.001**	**0.53**	
p-Value1	0.403	**<0.001**				
UDI-6						
Sham	17.4 (21.5)	14.7 (21.3)	−2.6 (9.6)	0.061	0.06	0.363
Active	24.0 (22.1)	15.9 (17.4)	−8.0 (15.3)	**0.003**	**0.14**	
p-Value1	0.229	0.532				

p-Value1, between-groups comparison at baseline and 4 months; *p*-Value2, within-group comparison before the laser treatment and after 4 months; *p*-Value3, between-groups comparison of differences. Statistically significant findings ($p < 0.05$) are presented in bold. Large effect ($\eta^2 > 0.14$) is presented in bold. FSFI, Female Sexual Function Index; GSM, genitourinary syndrome of menopause; SD, standard deviation; UDI-6, Urogenital Distress Inventory-6.

Discussion

This double-blind, sham-controlled, randomized trial provides evidence that CO_2-laser treatment is effective in reducing GSM bothersome symptoms. Specifically, this RCT verifies that active CO_2-laser treatment is superior to placebo for the management of GSM, a finding that up to this day could only be hypothesized. In the active group, all primary and secondary endpoints were significantly improved with large effect sizes, while in the sham group, dryness, itching, and burning was significantly improved with small or intermediate effect sizes. These results were further reflected by the proportion of participants with normal sexual function according to the FSFI, following the protocol completion (35.7% and 3% in the active group and sham group, respectively).

The findings of this study are markedly similar to those previously reported by observational studies[25–29]. In particular, the pooled improvement that was reported in a meta-analysis of observational studies regarding dyspareunia, vaginal dryness, and FSFI (total score and all domains) following

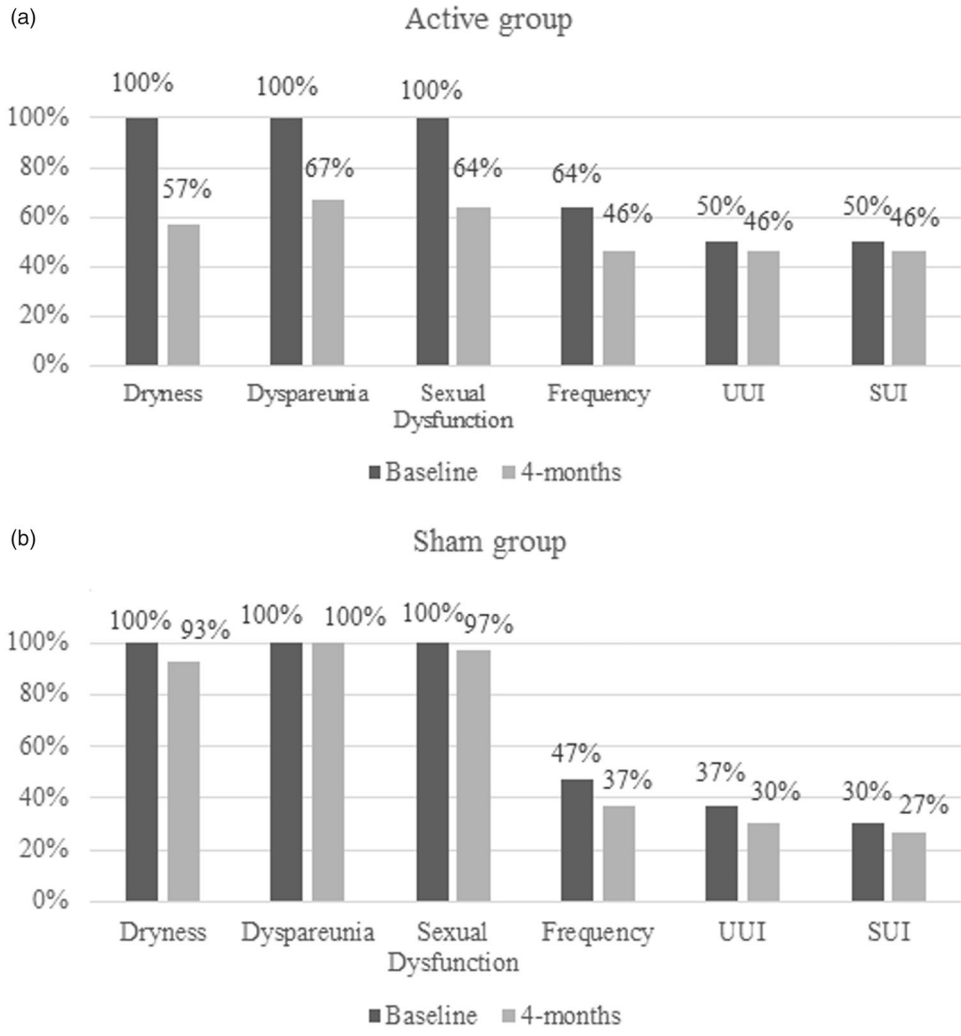

Figure 2. (a) Incidence (%) of dryness, dyspareunia, sexual dysfunction, frequency, urge urinary incontinence (UUI), and stress urinary incontinence (SUI) in the active group at baseline and 4-month follow-up. Dryness, dyspareunia, and sexual dysfunction incidence decreased significantly ($p = 0.0001$, $p = 0.0002$, and $p = 0.0007$, respectively). Incidence of urinary frequency, UUI, and SUI remained unchanged ($p = 0.28$, $p = 1$, and $p = 1$, respectively). (b) Incidence (%) of dryness, dyspareunia, sexual dysfunction, frequency, UUI, and SUI in the sham group at baseline and 4-month follow-up. All outcomes remained unchanged (all $p > 0.05$).

three CO_2-laser treatments was confirmed by this double-blind RCT[29]. Furthermore, the decrease in the incidence of sexual dysfunction following the completion of the current protocol was also in accordance with previous reports[7,30]. It must be noted that women included in this study, as in the prior ones, were 8–9 years since menopause with bothersome symptoms and sexual dysfunction indicating that CO_2-laser treatments may be proposed as monotherapy. However, this hypothesis cannot be supported by the results of another RCT that evaluated the efficacy of CO_2-laser treatments compared to vaginal estrogens[31]. Specifically, the results of the latter RCT suggested that CO_2-laser treatment combined with vaginal estrogens has a higher effectiveness than laser or estrogens alone[31]. This RCT applied only two CO_2-laser treatments and not three treatments as it is the standard protocol. Additionally, a placebo gel was administered in conjunction with CO_2-laser treatments. Any type of vaginal gel may have a hydration effect on vaginal mucosa that can affect the laser's absorption by the vaginal tissue and therefore might affect the laser's efficacy.

It is widely suggested that high-tech treatments produce a significant placebo effect, and this was confirmed by the results of the current study. In the sham group, the statistically significant decrease of dryness did not reflect a significant improvement in dyspareunia and sexual functioning. This finding may be explained by the hypothesis that a decrease of only 1.9 points on the 10-cm VAS, that was observed for dryness in the sham group, was not enough to produce significant changes in dyspareunia and sexual function improvement. Indeed, in the active group, dryness decreased significantly more (by 5.6 points) compared to the sham group. Additionally, this finding could be due to other factors than dryness that might be related to dyspareunia and sexual function, such as histopathological tissue changes. However, for this hypothesis to be confirmed, RCTs evaluating physio-pathological aspects of laser treatment in postmenopausal women with GSM are required.

Another interesting finding of this study is that, although the UDI-6 improved significantly in the active group but not in the sham group, there was no statistically significant difference in the between-group comparison. In addition, there was no difference in groups in terms of UF, UUI, and SUI incidence. A possible explanation for this result is that the proportion of the participants who experienced these symptoms

was up to 64% and, hence, differences from a statistical point of view could not be reached due to the small sample size. Furthermore, in a prior study it has been suggested that additional CO_2-laser treatments are needed for a statistically significant decrease in UF and incontinence incidence to be reached[30]. The current study confirms the latter, as three CO_2-laser treatments may not be adequate for the resolution of lower urinary tract symptoms (LUTS). This has to be further clarified in future studies focusing on postmenopausal women with LUTS as the most bothersome symptoms.

A strength of this RCT is its high methodological quality using a priori sample size calculation, block randomization, allocation concealment, and blinding of participants and evaluators. Another strength of this study is the use of strict inclusion criteria. In addition, sexual functioning was evaluated by the FSFI that has been validated to assess all aspects of sexual functioning and distinguish women with sexual dysfunction from those with normal sexual function. The FSFI does not assess female sexual distress, as the Female Sexual Distress Scale does. The latter could be a limitation of this study, as could also be the use of the 10-cm VAS. The VAS has not been validated in GSM symptoms and does not reflect how 'annoying' these GSM symptoms are to the patients. Nevertheless, it has been validated in women with dyspareunia due to endometriosis[32], it is the 'gold standard' of pain measurement, and it has been used in studies evaluating lubricants, moisturizers, vaginal estrogens, and laser treatments[28,33–35]. Thus, the results of this RCT can be directly compared to previous studies of other treatment strategies. Another limitation of this study is that all women had to have bothersome dryness and dyspareunia, while the presence of other GSM symptoms (i.e. LUTS) was not an inclusionary requirement. The latter resulted in a smaller sample size than appropriate to detect differences than was described in the statistical analysis. Nevertheless, the most bothersome symptom approach is suggested by the literature when it comes to GSM management[36]. Another limitation is that in the relatively short-term follow-up of 4 months we may not have yet seen the full effect of this regenerative treatment or any possible adverse events. Having said that, this is a typical time frame that has been used in placebo-controlled randomized trials evaluating local estrogens or ospemifene efficacy[37–41]. A further possible limitation of this study is that objective measurements of changes in the vaginal mucosa (i.e. Vaginal Health Index) were not used. We used only subjective measurements (i.e. 10-cm VAS, FSFI, etc.) based on the rationale that there is a good correlation between visual improvements in the vaginal mucosa and VVA symptoms[40].

Conclusions

The CO_2 laser is effective for the management of GSM symptoms in cases where dryness, dyspareunia, and sexual dysfunction are the most bothersome symptoms. This improvement is not the result of a placebo effect as the active laser treatments were found superior to the sham treatments. Bearing this in mind, our results should be interpreted with caution as they are derived from a short-term follow-up. In addition, further high-quality research is required to define the utility of CO_2 laser in other GSM symptoms such as LUTS, as well as the pathophysiological mechanism of its mode of action.

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