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Fractional CO_2 laser versus promestriene and lubricant in genitourinary syndrome of menopause: a randomized clinical trial

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Abstract

Objective: The aim of this study was to compare the effects of fractional CO_2 laser therapy, promestriene, and vaginal lubricants on genitourinary syndrome treatment and sexual function in postmenopausal women.

Methods: We performed a randomized clinical trial including 72 postmenopausal women over the age of 50 years. The women were randomized into three intervention groups to receive one of the following treatments: three sessions of intravaginal fractional CO_2 laser therapy; 10 mg of intravaginal promestriene cream 3 times a week; and vaginal lubricant application alone. Vaginal maturation, Vaginal Health Index (VHI) score, and Female Sexual Function Index (FSFI) were evaluated at baseline and after 14 weeks of therapy.

Results: We observed an improvement in the vaginal elasticity, volume, moisture, and pH in the CO_2 laser and promestriene groups. The VHI score at 14 weeks was higher in the CO_2 laser group (mean score 18.68) than in the promestriene (15.11) and lubricant (10.44) groups ($P < 0.001$). Regarding vaginal maturation, basal cells were reduced and superficial cells were increased after treatment. This improvement was more significant in the CO_2 laser group ($P < 0.001$). The FSFI score only showed improvement in the desire and lubrication domains in the CO_2 laser group. There were no differences in total FSFI score among the three treatment groups. There were no adverse effects associated with any of the treatments.

Conclusions: The use of fractional CO_2 laser therapy to treat genitourinary syndrome resulted in better short-term effects than those of promestriene or lubricant with respect to improving the vaginal health in postmenopausal women.

Key Words: CO_2 laser – Dyspareunia – Female sexual function – Genitourinary syndrome – Postmenopausal – Promestriene – Vulvovaginal atrophy.

Genitourinary syndrome of menopause (GSM) is characterized by a variety of menopausal, genital (dryness, burning, and irritation), sexual (lack of lubrication, discomfort/pain, impaired function), and urinary symptoms (urgency, dysuria). GSM, a new term, was created to replace vulvovaginal atrophy (VVA) because it is more accurate, all-encompassing, and acceptable to patients.[1-3]

Decreased circulating estrogen causes thinning of the vaginal epithelium, reduces its collagen content and hyalinization, decreases its elastin content, increases the connective tissue density, and reduces the vascularity of the vagina. These changes can lead to dyspareunia, burning, fissuring, and postcoital bleeding, and can negatively affect sexual function.[1]

Topical estrogens are the most common and effective treatments for GSM symptoms and can be administered in several forms, including creams, tablets, suppositories, and rings; however, no specific treatment regimen has been shown to be superior to others.[4] The beneficial effects are more evident during the therapeutic administration only.[5] The safety of low-dose vaginal estrogen therapy (ET) is concerning to survivors of estrogen-dependent neoplasias. In these women, nonhormonal vaginal lubricants and moisturizers used during sexual intercourse may be preferred as an initial therapy.[6-8]

In 2014, the SmartXide CO_2 laser was cleared by the US Food and Drug Administration (FDA) for ''incision, excision, vaporization and coagulation of body soft tissue in medical specialties including gynecology.''[9] In 2014, Salvatore et al performed the first pilot study using the fractional CO_2 laser to treat vaginal atrophy. They reported an improvement in GSM symptoms among postmenopausal women.[10] Additional laser systems have since become available for the treatment of GSM.[11]

Current GSM treatments, although effective in the short term, are associated with relapses and low compliance rates.

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Thus, new therapeutic options are needed to overcome the inconvenience of vaginal administration, poor efficacy rates, and potential contraindications to VVA of current therapies. Although laser technology seems to be another option for treating GSM, long-term efficacy and safety data remain scarce; the available data are primarily from observational studies with no comparison groups and only short-term follow-up. Despite this, vaginal lasers in clinical practice have been disseminated and this practice received strong criticism from regulatory agencies such as the FDA,[12] and the criticism was further endorsed by medical societies such as The North American Menopause Society (NAMS).[13]

Thus, well-designed research to better delineate specific applications of this technology is desirable before advocating its universal use for the treatment of GSM. Currently, there are no studies comparing vaginal promestriene with vaginal laser therapy for GSM or sexual function. Therefore, our objective was to compare the effects of fractional CO_2 laser therapy, vaginal promestriene, and vaginal lubricants in the treatment of genitourinary syndrome and sexual function in postmenopausal women.

METHODS

Sample size

At the time that this protocol was developed, there were no studies comparing CO_2 lasers with estrogen and vaginal lubricant therapies. Thus, results of open prospective pilot intervention study using fractional CO_2 laser treatment showed changes in Vaginal Health Index (VHI) before and after treatment were used as the basis for the present study protocol.[16] The number of patients needed for the study was calculated based on a standard deviation (SD) of 2.5, a difference of 2 points in the VHI, a significance level of 5%, and a power of 80%. To account for the potential loss of participants during the follow-up period, an initial sample of at least 20 patients was adopted for each group. A post hoc analysis was also performed, and the power of the sample was calculated based on the data obtained to evaluate the effect of CO_2 laser compared with other treatment regimens. Comparisons were based on the changes in total VHI score, which led to a power of 0.999, considering mean values of VHI (M), standard deviations (SD), and mean square errors (MSE) of the numerical variable deltas (single degree of freedom contrast in one-way analysis of variance [ANOVA]); thus, the alpha level of significance was set at 5%.

Study design and participants

A randomized controlled clinical trial comparing three treatment groups that were followed for 14 weeks was performed. This study was conducted at the Women's Health Hospital at the University of Campinas, Brazil, between March 2017 and November 2018. The study protocol was approved by the Ethics Committee of the Faculty of Medical Sciences-UNICAMP (number CAAE: 56634016.0.0000.5404). CONSORT guidelines were observed, and the study was cataloged in the Brazil Platform and Registry of Clinical Trials (Rebec) under the UTN identifier U1111-1220-1620. All participants signed an informed consent form before the start of data collection.

Seventy-two postmenopausal women were enrolled from the UNICAMP Menopause Outpatient Clinic, social media, or were patients at an outpatient clinic associated with the first author (C.A.P.). The inclusion criteria were the following: women aged 50 to 70 years; physiological amenorrhea for at least 12 months; symptoms of vaginal dryness with or without dyspareunia, vaginal burning, or pruritus; and no use of hormonal medications to treat vaginal symptoms in the prior 6 months. Participants were excluded for any of the following reasons: previous bilateral oophorectomy; body mass index (BMI) <18.5 or $>30\ kg/m^2$; contraindications to local estrogen use, including recent myocardial infarction, severe hypertension, diabetes mellitus, thromboembolic disorders, previous breast or endometrial cancer, or abnormal postmenopausal bleeding. Women undergoing behavioral treatment for depression or taking antidepressant medications, those with any other psychiatric disorders, HIV-positive women on antiretroviral therapy, women with a history of previous radiation therapy, and women with prior surgery for stress urinary incontinence were also excluded.

Study interventions and randomization

Seventy-two women were randomly assigned to one of the three treatment groups. Thus, 24 women in each group received one of the following treatments for 12 weeks:

- Intravaginal fractional CO_2 laser: three sessions performed at 30-day intervals (using the SmartXide^2 V^{2}LR, Monalisa Touch [DEKA Laser, Florence, Italy]).
- Vaginal cream containing promestriene: one vaginal applicator containing 1 g of cream and 10 mg of promestriene (Eurofarma Laboratorie S.A, Brazil) administered 3 times a week.
- Lubricant gel: water-based lubricant (KY—Johnson & Johnson, New Brunswick, NJ) applied with sexual activity.

The participants were randomized to one of the three treatments in a 1:1:1 ratio based on a computer-generated randomization list that was prepared by a statistician. The participant numbers and treatment codes were assigned after confirming the inclusion and exclusion criteria.

Procedures

Laser treatment

The laser procedures were performed in an outpatient clinic associated with the first author (C.A.P.) using the SmartXide^2 V^{2}LR, Monalisa Touch (DEKA) fractional microablative CO_2 laser which was rented by the clinic. The laser equipment was rented for use on the days the research participants were seen and was used on clinic patients as well as the women participating in the study. Prior to performing the procedure, participants did not require any specific preparation (eg, analgesia/anesthesia). The participant was placed in dorsal lithotomy position, a vaginal speculum was inserted, and the vaginal wall secretions were removed. Next, the vaginal length measured in centimeter was evaluated and a 360°

cylindrical probe was introduced, which allowed the laser to reach the entire vaginal wall circumference. After introducing the probe, it was rotated and slowly withdrawn, with continuous use of the pedal according to the precalibrated marks on the probe. The laser was set to a power of 40 W, with a dwelling time of 1.000 μs, dot spacing of 1.000 μm, and a smart stack of 2.0.[16] Participants were advised to abstain from sexual activity for 10 days before treatment.

Study outcomes

The primary outcome was improvement in vaginal atrophy. The parameters used to evaluate vaginal health were as follows.

Vaginal Health Index

VHI scores accounted for the following five parameters: elasticity, fluid volume, pH, epithelial integrity, and moisture. Scores less than 15 were indicative of vaginal atrophy. Each parameter was graded from 1 (worst condition) to 5 (best condition) with a maximum possible score of 25 points. The ''elasticity'' parameter was mainly evaluated by introducing and positioning the speculum in the vaginal canal. Based on VVA severity, it was possible to identify reduced vaginal distensibility and increased pain during this examination. Cotton-tipped applicators pressed along the vaginal walls also provided information on vaginal ''elasticity.'' The ''epithelial integrity'' parameter was evaluated while introducing the speculum and observing the bleeding tendency of the vaginal walls. The ''vaginal pH'' was evaluated using a colorimetric test, and ''fluid volume'' was evaluated using a cotton-tipped applicator as it was passed over the vaginal walls.

Vaginal maturation

Vaginal smear samples were collected from the upper distal third of the right lateral wall using an Ayre spatula. Parabasal (P), intermediate (I), and superficial (S) cell counts were obtained to determine the degree of atrophy based on the Frost index. This index enabled us to objectively evaluate the differential count of each cell group expressed as a percentage. The greater the degree of vaginal atrophy, the greater the estrogen deficiency. When at most 30% of the deep cells were present in the vaginal smears, mild hypoestrogenism was diagnosed. A deep cell percentage between 30% and 49% indicated moderate hypoestrogenism and a more than 50% deep cell percentage indicated hypoestrogenism.[14]

Sexual function

The secondary outcome was sexual function, which was measured using the Female Sexual Function Index (FSFI). This questionnaire, which contains 19 items, was developed as a brief, but multidimensional, self-reporting instrument to assess the key dimensions of female sexual function. It was developed based on a group of normal female controls and age-matched women who met the DSM-IV-TR criteria for female sexual arousal disorder (FSAD). The FSFI addresses six domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain) and provides full-scale scores ranging from 2.0 (severe dysfunction) to 36.0 (absence of dysfunction). The validated FSFI version for the Portuguese language was used.[15] A cutoff score of 26.55, as reported by Wiegel et al,[16] was used to differentiate the presence or absence of sexual dysfunction.

Statistical analysis

Categorical variable frequency tables were created with absolute (n) and percentage (%) frequency values to describe the study population characteristics. For numerical variables, means and standard deviations were calculated. The analysis was performed using an intention-to-treat method with the last observation being carried forward (LOCF) in cases of missing follow-up data.

To compare the categorical variables among the three groups, chi-square or Fisher's exact tests were used (for expected values less than 5). The Kruskal–Wallis test was used to compare the numerical variables because of their nonnormal distribution. To compare the scores between the groups and between the baseline and posttreatment (14 wk) results, a repeated-measures ANOVA was performed. The ANOVA, followed by Tukey's and contrast profile tests, was performed, with variables transformed into positions/ranks due to the nondistribution. A covariance test (ANCOVA) for repeated measurements was used to compare the numerical variables between the three groups and between the time points, which were adjusted for race and educational level.

To compare the categorical variables before and after treatment, the McNemar test and the Bowker symmetry test were used for related samples. To compare numerical variables before and after treatment, the Wilcoxon test was used for related samples because of their non-normal distribution. The significance level for the statistical tests was set at 5%. The statistical analysis was performed using SAS for Windows, version 9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 267 women were recruited to participate in the study; however, only 72 met the inclusion criteria and were randomized into the three treatment groups (Fig. 1). The main reasons for exclusion of the other 195 women were current/past hormonal treatment users, recent vaginal treatments, and comorbidities that precluded study participation. The main characteristics of the study population are described in Table 1.

Of the 72 women enrolled, 2 women in the CO_2 laser group, 5 in the promestriene group, and 8 in the lubricant group discontinued the study before completing the 14 weeks. One woman assigned to the lubricant group discontinued participation because she developed allergic vaginitis in week 4; thus, the treatment was immediately discontinued. No other adverse effects were reported in the laser, promestriene, or lubricant treatment groups.

The mean ages of the women were 57.83 ± 5.01, 57.21 ± 5.26, and 56.79 ± 5.33 years in the laser, promestriene, and lubricant groups, respectively, and there was no significant intergroup difference ($P = 0.784$). There were no significant intergroup differences in the mean age of

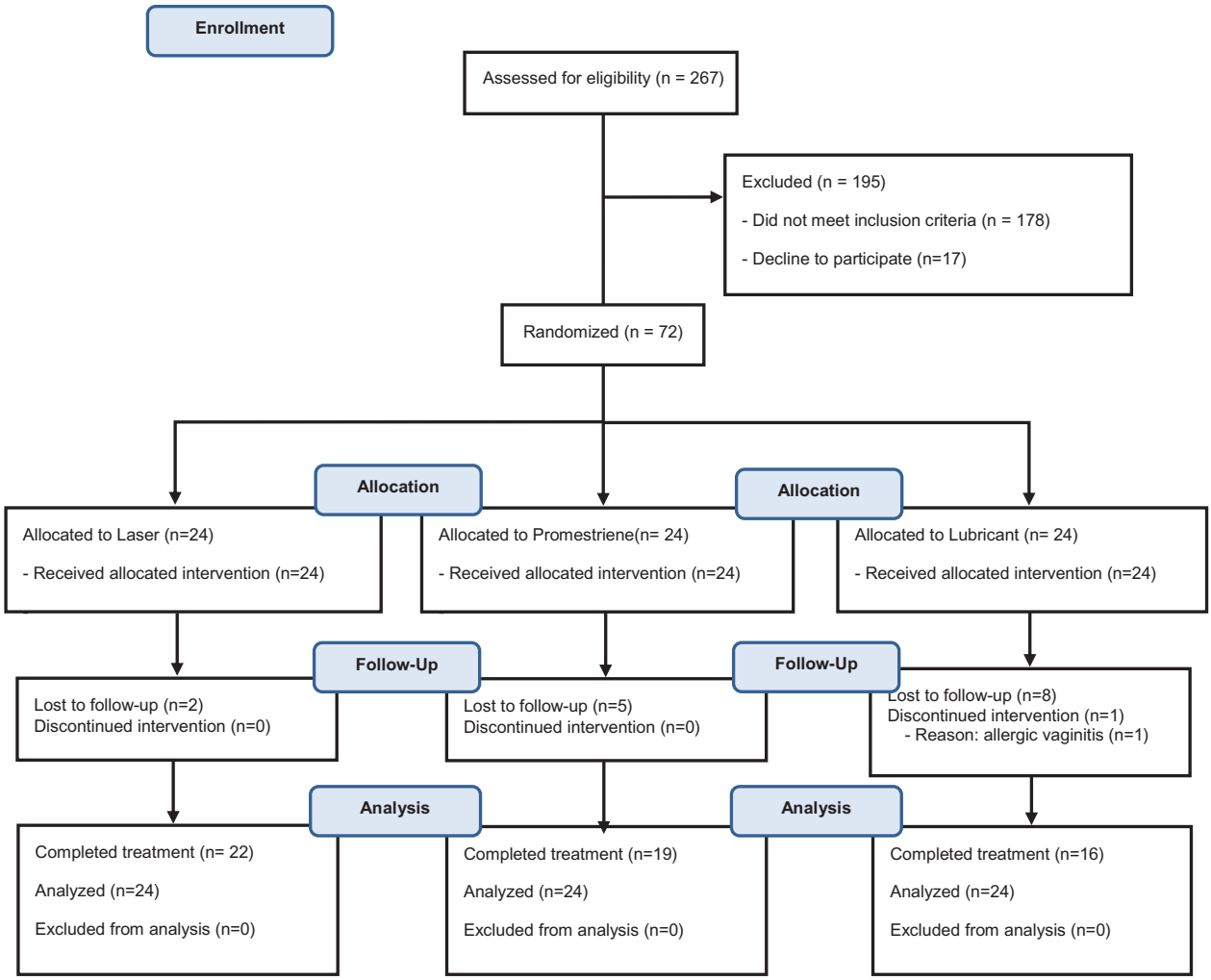

FIG. 1. CONSORT Flowchart of participants.[17]

menopause ($P = 0.446$). The majority of the participants declared themselves to be white, but there was a higher percentage of non-whites in the promestriene and lubricant groups ($P = 0.032$). Regarding education, in the promestriene group, the participants achieved lower educational levels ($P = 0.013$). The sociodemographic and clinical data are described in Table 1.

Table 2 shows the comparison of each parameter and the total VHI. The mean baseline for each of the five parameters and the total baseline score were low, and there were no statistically significant intergroup differences. The results of the treatments were determined at 14 weeks, and there were significant differences in the mean score for each isolated parameter. The results of the ANOVA showed improvements in elasticity ($F = 43.41$; $P < 0.001$), fluid volume ($F = 60.43$; $P < 0.001$), moisture ($F = 86.92$; $P < 0.001$), and epithelial integrity ($F = 43.54$; $P < 0.001$). The vaginal pH decreased to 3.98 in the CO_2 laser group, 4.89 in the promestriene group, and 5.75 in the lubricant group. The ANOVA showed that the results in each group differed significantly ($F = 7.43$; $P = 0.001$). There was also a statistically significant difference in the mean total pre- and post-VHI scores ($F = 126.98$; $P < 0.001$) and in the scores between the groups ($F = 4.40$; $P = 0.017$).

The highest score, 18.68 (± 3.20), was observed in the CO_2 laser group, followed by the promestriene and lubricant groups (15.11 [± 3.98] and 10.44 [± 2.78], respectively).

The VHI increases were as follows: the CO_2 group showed the greatest increase in VHI, followed by the promestriene and lubricant groups (9.36 [$\pm$ 3.40], 5.89 [$\pm$ 3.68], 0.06 [± 1.65], respectively). The pair-wise ANOVA testing confirmed that there were significant differences between the increases in each group (CO_2 vs promestriene $P = 0.003$; CO_2 vs lubricant $P < 0.001$; promestriene vs lubricant $P < 0.001$).

The Frost index of vaginal maturation showed significant differences in the percentage of basal cells before treatment. After treatment, there was a decrease in the percentage of basal cells and an increase in the percentage of intermediate and superficial cells, indicating an overall improvement in vaginal maturation ($P < 0.001$); this was more evident in the CO_2 laser group (Table 3).

TABLE 1. *Demographic and clinical characteristics of the study participants at baseline according to treatment group*

Characteristics	Laser (Mean ± DP)		Promestriene (Mean ± DP)		Lubricant (Mean ± DP)		*P*
Age, y	57.83 ± 5.01		57.21 ± 5.26		56.79 ± 5.33		0.784[a]
Years since menopause	9.35 ± 4.61		9.96 ± 7.35		8.58 ± 6.89		0.446[a]
Menopause age	48.91 ± 4.09		47.21 ± 6.62		48.33 ± 5.62		0.747[a]
	n	%	*n*	%	*n*	%	
Race							
White	23	95.83	16	66.67	17	70.83	0.032[b]
Non-white	1	4.17	8	33.33	7	29.17	
Education							
Elementary school	2	8.33	11	45.83	4	16.67	0.013[b]
High school	6	25.00	7	29.17	6	25.00	
High education	16	66.67	6	25.00	14	58.33	
Smoking							
Smoker/Ex-smoker	5	20.83	8	33.33	9	37.50	0.792[b]
Nonsmoker	19	79.17	16	66.67	15	62.50	
Parity							
0	1	4.16	3	12.50	2	8.33	0.865[b]
1	4	16.67	4	16.67	3	12.50	
≥ 2	19	79.17	17	70.83	19	79.17	
Marital status							
Single	0	0	3	12.50	2	8.33	0.148[b]
Married	16	66.67	18	75.00	19	79.17	
Divorced	8	33.33	3	12.50	3	12.50	
Profession							
Employed/paid worker	15	62.50	16	66.67	17	70.83	0.759[b]
Work at home	4	16.67	6	25.00	4	16.67	
Retired	5	20.83	2	8.33	3	12.50	

[a]*P* value for Kruskal–Wallis.
[b]*P* value chi-square or Fisher's exact test.

TABLE 2. *Vaginal Health Index score (VHI) at baseline and 14 weeks according to treatment group*

VHI	Laser mean (SD)	Promestriene mean (SD)	Lubricant mean (SD)	*P**
Elasticity				
Baseline	2.04 (0.55)	1.96 (0.55)	2.08 (0.65)	0.817
Week 14	3.41 (0.91)	2.58 (0.81)	2.19 (0.54)	**<0.001**
P baseline × week 14	**0.006**	**0.025**	0.970	
Δ baseline and week 14	1.36 (0.79)	0.58 (0.69)	0.00 (0.63)	**<0.001**[a]
Fluid volume				
Baseline	1.92 (0.58)	1.79 (0.66)	1.92 (0.72)	0.736
Week 14	3.41 (0.73)	2.79 (0.99)	2.00 (0.63)	**<0.001**
P baseline × week 14	**0.029**	**0.030**	0.572	
Δ baseline and week 14	1.50 (0.91)	1.05 (0.85)	−0.13 (0.62)	**<0.001**[b]
pH				
Baseline	6.33 (0.64)	6.21 (0.66)	6.17 (0.70)	0.799
Week 14	3.98 (0.59)	4.89 (0.94)	5.75 (0.58)	**<0.001**
P baseline × week 14	**0.001**	**0.043**	0.262	
Δ baseline and week 14	−2.38 (0.93)	−1.32 (1.34)	−0.31 (0.87)	**<0.001**[c]
Moisture				
Baseline	2.17 (0.92)	1.83 (0.70)	2.04 (0.75)	0.799
Week 14	3.98 (0.59)	3.11 (0.88)	2.13 (0.89)	**<0.001**
P baseline × week 14	**0.036**	**0.030**	0.392	
Δ baseline and week 14	1.45 (1.26)	1.16 (0.76)	−0.06 (0.57)	**<0.001**[d]
Epithelial integrity				
Baseline	2.00 (0.66)	1.92 (0.50)	2.00 (0.66)	0.868
Week 14	3.68 (0.99)	3.00 (0.88)	2.13 (0.72)	**<0.001**
P baseline × week 14	**<0.001**	**<0.001**	1.00	
Δ baseline and week 14	1.73 (1.03)	1.05 (0.78)	0.19 (0.40)	**<0.001**[e]
Total				
Baseline	9.50 (2.59)	9.00 (2.52)	9.79 (3.09)	0.836
Week 14	18.68 (3.20)	15.11 (3.98)	10.44 (2.78)	**<0.001**
P baseline × week 14	**<0.001**	**<0.001**	1.00	
Δ baseline and week 14	9.36 (3.40)	5.89 (3.68)	0.06 (1.65)	**<0.001**[f,g]

Significant *P* values ($P < 0.05$) are highlighted in bold font.
∗*P* value for the Kruskal–Wallis test Laser ≠Promestriene; Laser≠ Lubricant, Promestriene ≠ Lubricant.
[a,b,c,d,e,f]ANCOVAs test for repeated measurements to compare the numerical variables between the three groups and between the 2 times, adjusted for race and education.
[g]Laser ≠ promestriene; laser ≠ lubricant; promestriene ≠ lubricant ($P < 0.001$).

TABLE 3. *Frost index at baseline and 14 weeks according to treatment group*

Cells	Laser mean (SD)	Promestriene mean (SD)	Lubrificant mean (SD)	P^*
Basal				
Baseline	27.23 (17.20)	27.84 (22.62)	37.00 (21.69)	**0.044**
Week 14	5.82 (4.23)	20.84 (23.39)	40.19 (18.10)	**<0.001**
P baseline × week 14	**<0.001**	0.080	0.537	
Δ baseline and week 14	−21.41 (16.50)	−7.00 (10.36)	3.19 (23.26)	**<0.001**[a]
Intermediary				
Baseline	73.45 (16.72)	71.89 (22.67)	61.50 (24.15)	**0.027**
Week 14	88.73 (5.81)	77.68 (22.66)	58.88 (18.24)	**<0.001**
P baseline × week 14	**<0.001**	0.042	0.715	
Δ baseline and week 14	15.27 (14.98)	5.79 (10.86)	−2.63 (26.75)	**<0.001**[b,c]
Superficial				
Baseline	0.50 (1.74)	0.26 (1.15)	0.25 (0.77)	0.877
Week 14	5.00 (3.83)	2.00 (2.62)	0.31 (1.25)	**<0.001**
P baseline × week 14	**<0.001**	**0.004**	1.000	
Δ baseline and week 14	4.50 (4.27)	1.74 (2.56)	0.06 (1.53)	**<0.001**[d]

Significant *P* values ($P < 0.05$) are highlighted in bold font.
*P value for the Kruskal–Wallis test.
[a,b,c]ANCOVAs test for repeated measurements to compare the numerical variables between the three groups and between the 2 times, adjusted for race and education.
[a]P Laser ≠Promestriene and Laser ≠Lubricant ($P<0.001$).
[b]P Laser ≠Lubricant ($P=0.031$).
[c]P Promestriene ≠ Lubricant ($P<0.001$).

On analyzing the FSFI, we observed some improvements in isolated sexual function domains by group: the desire and lubrication domains showed improvement in the laser group and the orgasm and satisfaction domains showed improvement in the lubricant group. There were no significant differences in the total score for each of the domains of sexual function between the three treatment groups (Table 4).

TABLE 4. *Sexual Function Questionnaire Score – FSFI score at baseline and 14 weeks according to treatment group*

FSFI domain	Laser mean (SD)	Promestriene mean (SD)	Lubricant mean (SD)	P^*
Desire				
Baseline	2.80 (1.20)	2.83 (1.24)	2.98 (1.45)	0.643
Week 14	3.16 (1.19)	2.97 (0.93)	2.89 (1.09)	
P (baseline × week 14)	**0.047**	0.910	0.406	
Δ baseline and week 14	0.41 (0.86)	−0.03 (1.07)	0.28 (0.93)	0.071[a]
Arousal				
Baseline	2.95 (1.80)	2.64 (1.87)	2.63 (1.77)	0.628
Week 14	3.22 (1.61)	2.87 (1.83)	2.93 (1.52)	
P (baseline × week 14)	0.533	0.417	0.399	
Δ baseline and week 14	0.23 (1.60)	0.19 (1.54)	0.42 (1.54)	0.0823[b]
Lubrication				
Baseline	2.46 (1.74)	2.00 (1.46)	2.44 (1.65)	0.234
Week 14	3.59 (1.94)	2.75 (2.02)	2.86 (1.44)	
P (baseline × week 14)	**0.011**	0.139	0.051	
Δ baseline and week 14	1.02 (1.94)	0.69 (1.82)	0.58 (1.09)	0.295[c]
Orgasm				
Baseline	2.93 (1.96)	2.85 (1.89)	2.67 (1.93)	0.404
Week 14	3.64 (1.96)	2.86 (2.14)	3.39 (1.74)	
P (baseline × week 14)	0.061	0.808	**0.014**	
Δ baseline and week 14	0.62 (2.14)	−0.13 (1.88)	0.89 (1.31)	0.175[d]
Satisfaction				
Baseline	3.58 (1.55)	3.30 (1.62)	3.13 (1.48)	0.918
Week 14	3.76 (1.53)	3.96 (1.58)	4.00 (1.37)	
P (baseline × week 14)	0.351	0.098	**0.038**	
Δ baseline and week 14	0.20 2.06	0.67 1.50	0.92 1.52	0.562[e]
Pain				
Baseline	2.55 (1.85)	1.73 (1.50)	2.00 (1.80)	0.202
Week 14	3.18 (2.39)	2.63 (2.09)	1.72 (1.07)	
P (baseline × week 14)	0.456	0.188	0.969	
Δ baseline and week 14	0.47 (2.36)	0.59 (1.95)	−0.05 (1.16)	0.978[f]
Total				
Baseline	17.28 (8.46)	15.35 (7.57)	15.84 (7.66)	0.396
Week 14	20.55 (8.68)	18.04 (9.46)	17.79 (7.13)	
P (baseline × week 14)	0.134	0.182	**0.038**	
Δ baseline and week 14	2.95 (8.92)	1.99 (7.74)	3.05 (5.59)	0.577[g]

Significant *P* values ($P < 0.05$) are highlighted in bold font.
*P value for the Kruskal–Wallis test to compare values between the three groups.
[a,b,c,d,e,f,g]ANCOVA test for repeated measurements to compare the numerical variables between the three groups and between the 2 times, adjusted for race and education.

DISCUSSION

In this study, we compared the effects of fractional CO_2 laser therapy to those of well-established postmenopausal GSM and sexual function treatments, and found that laser therapy was effective for improving vaginal parameters in postmenopausal women.

Laser treatments are increasingly being used by gynecologists. Currently, two laser technologies, microablative fractional CO_2 lasers and nonablative photothermal Erbium:YAG lasers, have been used to treat postmenopausal women with GSM. A number of studies have shown that lasers are efficacious for reversing vaginal atrophy related to menopause.[11,12,18-22] Most studies remain open, have small numbers of participants, and only short-term follow-up.[18]

In the present study, vaginal health, measured objectively using the VHI scoring system, was improved in all five parameters (overall elasticity, fluid secretion type, pH, epithelial integrity, and moisture) after the treatments. There was a greater increase in total VHI after CO_2 laser therapy compared with that after vaginal ET, the current gold standard treatment for VVA.[23,24]

After treatment, there was a significant decrease in vaginal pH, reaching normal levels (between 3.8 and 4.5) in the CO_2 laser and promestriene groups. This indicated normalization of vaginal health, which did not occur in the lubricant group. Lubricants helped to reduce friction and irritation during sexual activity, but did not correct any of the vaginal parameters or provide long-term benefits. Our maturation cell index results demonstrated improved cytological patterns with significant decreases in basal cells and increases in superficial cells that were more pronounced in the laser group. In the present study, the improvements were largely observed in the ''objective'' measures of vaginal health (cell maturation, vaginal health score), which do not necessarily indicate an improvement in patient's complaints or symptoms.

Our results corroborate those obtained by Gaspar et al (2017), whose prospective open study compared the effects of the Erbium laser with vaginal estriol. They observed greater vaginal maturation after laser treatments than after estriol treatments. They emphasized that despite initial improvements in vaginal maturation with estriol use, the beneficial effects began to decrease after 3 months. In the laser group, the improvement was, however, greater and lasted up to 12 months.[25]

A recent systematic review of vaginal laser therapy included 14 eligible studies with 542 participants. All the studies were prospective, uncontrolled, and compared the women's symptoms before and after treatment. Laser therapy was used to treat sexual dysfunction and vaginal symptoms, including dryness, dyspareunia, and itching. The quality of the evidence was, however, ''low'' or ''very low'' because no randomized controlled trials were included. Those authors concluded that changes to the clinical management of GSM could not be proposed based on the available evidence in the literature.[18]

The first double-blind randomized study by Cruz et al in 2018 compared CO_2 laser alone, estrogen alone, and a combination of laser and local ET. They showed that the fractional CO_2 laser plus local estrogen seemed to be effective and advantageous for improving vaginal health.[22]

Regarding sexual function, we observed a significant improvement in the desire and lubrication domains in the laser group, but there was no significant difference in the total FSFI score between the three treatment groups. After treatment, the total score increased by about 3 points in the laser and promestriene groups, but this difference was not significant. The scores remained below the threshold value of 26.55, which defines sexual dysfunction.[16]

Most studies of laser therapy showed slight improvements in sexual function after the therapy, although most women continued to have sexual dysfunction according to their FSFI scores. Many women, who had previously ceased engaging in sexual activity due to their vaginal symptoms, however, resumed their sex lives after laser treatment.[18] Differences in our study results and those of other studies may result from methodological differences (methods of measuring sexual function in clinical trials,[26] sample sizes, and populations); however, it is important to emphasize that sexual function is complex and can be affected by many factors in all age ranges. In climacteric women, the problems can become worse secondary to dyspareunia, decreased desire and arousal, longer relationships, and changes in body image.[26–28]

In our study, there were no adverse effects after the laser therapy. Gambacini et al reported that fewer than 3% of women discontinued therapy because of adverse effects and the beneficial effects of their laser therapy persisted for 18 to 24 months.[29,30]

The small number of participants and short-term follow-up are the main limitations to this study. Another potential limitation is that we did not include a sham laser (placebo) group for ethical reasons. Our local ethics committee suggested that some form of intervention should be used instead of placebo. The lubrication group served this purpose in our study. Although changes in vaginal health scores are not expected when lubricants are used alone, slight changes in the sexual response could occur when lubricants are used during sexual intercourse; however, this was not observed in the present study. Despite these limitations, we consider our findings to be relevant and they highlight the need for new alternatives in the treatment of GSM. We conducted a randomized clinical trial to compare a new technology with conventional treatments and the results are consistent and provide level A evidence for the efficacy of lasers in the treatment of GSM, a condition with high prevalence among postmenopausal women.

CONCLUSIONS

The use of fractional CO_2 laser therapy to treat genitourinary syndrome resulted in better short-term effects than those of promestriene or lubricant with respect to improving the vaginal health in postmenopausal women. Randomized

studies with long-term follow-up and adequate sample sizes are needed to compare the effects of laser treatments to other therapies and to provide evidence for incorporating this technology into routine clinical practice.

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