

Efficacy of a Mixed Wavelength Laser for Vaginal Health in Postmenopausal Women: A Randomized Controlled Trial

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Background: Genitourinary syndrome of menopause (GSM) is a chronic and progressive condition. The adverse events (AEs) and contraindications of hormonal therapy have generated interest in vaginal laser treatment. The non-ablative wavelength 1540 nm (GaAs) in this mixed laser synergistically enhances the 10,600 nm (CO₂) effect, providing a deeper hyperthermic stimulation of collagen and elastin without damaging the superficial layers. This results in fewer AEs, and reverses vaginal atrophy (VA) while reducing the 10,600 nm laser power to 5W. The aim of the study is to evaluate the efficacy and safety of a mixed-wavelength laser in alleviating GSM symptoms compared to sham.

Patients and Methods: A randomized single-blind sham-controlled trial was conducted. 31 postmenopausal women with Vaginal Maturation Value (VMV <50%) were randomized into laser or sham intervention groups, receiving three monthly treatments. VMV, vaginal pH, and GSM symptoms severity were measured at 3- and 9-months post-intervention, and AE were assessed.

Results: 27 patients completed the study; 14 were randomly assigned to the laser and 13 to the sham group. At 3 months, VMV improved by 12.4% compared to the sham group ($P = 0.033$), indicating a significant reversal of VA and a significant patient global improvement ($P = 0.030$). At 9 months, dyspareunia decreased significantly ($P = 0.049$), while other symptoms and patient satisfaction demonstrated a significant improvement trend. However, VMV in the laser group returned to baseline values. Vaginal pH remained unchanged. The laser intervention was well tolerated, with mild and self-limited AEs.

Conclusion: The mixed wavelength laser enables a reduction of 10,600 nm laser power, enhancing its safety profile while achieving promising outcomes in GSM. It is a safe, well-tolerated, and effective alternative for GSM treatment when conventional therapies fail. Further studies with larger samples, varied settings, and extended follow-up are needed to assess its long-term efficacy and side effects.

Keywords: vaginal rejuvenation, vaginal atrophy, genitourinary syndrome of menopause, hybrid laser, 1,540 nm, non-ablative laser

Introduction

Genitourinary Syndrome of Menopause (GSM) is a chronic and progressive condition¹ caused by a decline in estrogen levels during menopause or other medical diseases. It manifests with symptoms such as vaginal dryness, dyspareunia, burning, itching, and urinary symptoms, among others, that significantly impact physical, psychological, and sexual well-being.^{2,3} The prevalence of GSM varies across studies, with worldwide estimates ranging from 50% to 70–84.2%, as reported in two European studies.^{4,5}

An additional at-risk group includes breast cancer (BC) patients, as the hypoestrogenic state induced by BC treatments is more strongly associated with the development of GSM than natural menopause.^{6,7}

To restore vaginal health, the first-line treatment includes moisturizers and lubricants, with topical estrogens as the second-line option. Other therapies have also emerged: hyaluronic acid, plasma-rich platelets, and energy-based

devices like radiofrequency.^{8–14} However, in recent years, laser technology has also demonstrated beneficial effects on vaginal atrophy due to its minimal side effects, status as an office-based procedure, and reduced recovery time.¹⁵ In patients experiencing adverse effects or contraindications, such as BC patients, Ospemifene has been proven to be safe and effective.^{16,17} Additionally, Ospemifene has demonstrated good results in overactive bladder associated with GSM.¹⁶ The commonly used lasers for GSM include the ablative 10,600 nm wavelength and the Er: YAG laser wavelength 2940 nm used in a non-ablative mode.¹⁸ These wavelengths have an affinity for intracellular water in the vagina but possess limited tissue depth penetration.¹⁹ Ablative lasers vaporize superficial tissue and are known to be more effective and aggressive than non-ablative lasers.

The 1540 nm wavelength in the mixed laser has a lower affinity for water, preventing heat from concentrating in the superficial layers. This reduces damage to these layers while creating microthermal columns that penetrate up to 2.5 mm into the tissue,²⁰ stimulating neocollagenesis and promoting deeper elastin deposition.^{21,22} However, its effectiveness remains limited compared to ablative lasers, and further studies are needed to assess long-term outcomes.²³

The combination of the 1540 nm and 10,600 nm lasers enhances the thermal and coagulation effects on treated tissues. This approach allows for a reduction in 10,600 nm laser power, minimizing vaginal mucosa ablation while achieving greater tissue shrinkage and better results, with reduced risks and side effects compared to 10,600 nm laser treatment alone.²⁰ However, to date, there is only one publication in gynecology with this combination of wavelengths on female sexual function and urinary incontinence, and none in GSM.²⁴

VMV and vaginal pH associated with GSM are objective measures to evaluate the impact of different therapies on vaginal atrophy.^{25,26}

We conducted a parallel randomized controlled trial to minimize bias and ensure that the observed effects could be directly attributed to the intervention. The study aimed to assess the efficacy and safety of combined 10,600 nm and 1540 nm laser therapy, using a reduced 10,600 nm power of 5 W, to improve VMV and alleviate GSM symptoms in postmenopausal women who were refractory to first-line topical treatments.

Materials and Methods

We conducted a prospective randomized parallel single-blind sham-controlled trial at the Hospital Universitari Sant Joan de Reus, Spain, from May 2019 to August 2021. Individuals who attended the menopause clinic at Hospital Sant Joan de Reus, and its affiliated health centers, presenting GSM symptoms, were invited to participate in the study. Detailed information about the study was provided through an informational pamphlet, and participants provided signed informed consent on the first day of the study initiation prior to enrollment at the hospital.

Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed.

Participants

Menopausal women up to 65 years old are diagnosed with spontaneous or iatrogenic menopause, according to the NICE guideline (NG23).²⁷

Inclusion Criteria

Participants were required to have at least one symptom of the GSM, such as vaginal dryness, burning, itching, or dyspareunia, with a VMV <50%, and have failed first and second-line treatment. The VMV was obtained on the first day of the study at the menopausal outpatient clinics of the hospital. Patients who met the inclusion criteria were scheduled for randomization.

Exclusion Criteria

VMV $\geq$ 50%, hormone replacement therapy, previous use of topical estrogen, moisturizers, lubricants, or probiotics 3 months before enrollment, the impossibility of introducing the laser device, previous pelvic radiotherapy, gynecologic or rectal cancer less than 5 years ago, breast cancer patients, insulin-dependent diabetes mellitus (IDDM) or non-dependent insulin poorly controlled, Body Mass Index (BMI) > 40 kg/m², women who present active or recurrent genital herpes.

Eligible participants were randomized using the website Randomization.com (<http://www.randomization.com>). The randomization generated a list of treatments, assigning participants to either the laser or sham intervention at a 1:1 ratio based on the order of their entry into the study. The list was securely locked and accessible only to the lead investigator (J.S.P) during the intervention, who was the only individual aware of the intervention allocation. The laser in sham mode emitted the same sound and had the same duration as the active mode, ensuring the patient blinding. The cytologists (C. G.C) and other investigators (S.T, P.C.B) remained blinded to all clinical information.

Intervention

The adherence to the protocol was ensured as the trained lead investigator was the only person responsible for implementing the treatment protocol. This consisted of one laser or sham treatment administered monthly for three consecutive months, as previously described by Mezzana.²⁴ Both the standard treatment and the protocols for reducing energy in case of intolerance were programmed into the laser hardware, ensuring consistent treatment across patients. The intervention was performed with mixed laser wavelengths 1540 nm –10,600 nm (Shelase, Youlaser MT, Quanta System S.p.A Via Acquedotto, 109, 21017 Samarate, Italy), and the laser intervention settings were as follows:

- a. The first pulse of 1540 nm: at 8W for 14 ms and 1 ms delay.
- b. The second pulse of 10,600 nm: at 5W for 3ms.
- c. Dot density: 150 dot/cm².
- d. Energy 127,0 mJ/dot.

The sham intervention followed the same procedure but with 0W power. Both interventions were performed without topical anesthesia.

The procedure involved drying the vagina with a swab, followed by the gentle insertion of a vaginal probe emitting laser in a 360° pattern (two passes with a 30° rotation).

Laser treatment of the vaginal introitus was omitted.

To aid a vaginal recovery reepithelization, patients were instructed to apply a Melagyn® ovule Gynea, containing (aloe barbadensis oily extract, colloidal silica, lactic acid, potassium chloride, disodium edetate, poly (hexamethylene) biguanide hydrochloride (PHMB), semisynthetic glycerides and purified water) for three consecutive days after each intervention.

The primary outcome assessed was the VMV at baseline, 3 and 9 months after the laser or sham intervention. Secondary outcomes included changes in vaginal pH and the evaluation of subjective symptoms.

Objective Assessment Measures for GSM

VMV

A vaginal smear was obtained from the lateral vaginal wall using a cytobrush and placed in a liquid cytology PreservCyt solution. The sample was processed by ThinPrep5000 and analyzed by the same certified cytopathologist.

VMV was evaluated by determining the percentage of superficial, intermediate, and parabasal epithelial cells on the smear. The VMV was calculated using the formula $[(1 \times \% \text{ superficial}) + (0,5 \times \% \text{ intermediate}) + (0 \times \% \text{ parabasal})]$ expressed as a percentage.²⁸

VMV was categorized into 3 groups: values 0–49%, 50–64%, and 65–100%, representing absent/low, moderate, and high estrogenic effects on the vaginal epithelium, respectively.

Vaginal pH

Vaginal pH was measured using color-fixed indicator sticks ranging from pH 0–14 (pH ≥ 5 indicated vaginal atrophy, pH < 5 indicated good estrogenization).²⁹

Subjective Assessment Measures for GSM

The patients completed the VAS for GSM symptoms, PGI, and PGS questionnaires at home and submitted their responses to the collaborating researchers with no possibility of alterations. The principal investigator did not have access to the results.

1. Visual Analogue Scale (VAS 0–10): GSM symptoms (vaginal dryness, itching, burning, dyspareunia, and dysuria) were assessed using a VAS ranging from 0 (absence of symptoms) to 10 (severe symptoms). Scores <4 indicated mild symptoms, scores ≥ 4 to <8 moderate symptoms, and ≥ 8 severe symptoms.
2. VAS for pain (0–10): pain experienced during the intervention was assessed using a VAS, with (0) indicating no pain, (1–3) mild pain, (4–6) moderate pain, and (7–10) severe pain.
3. Patient's Global Impression of Improvement Questionnaire (PGI): a Likert scale questionnaire was used to assess the patient's perception of improvement in GSM symptoms, ranging from 1 (very much worse) to 7 (very much better). A favorable response was considered if the rating indicated an improvement from better to very much better.
4. Patients' Global Satisfaction (PGS) with the treatment was evaluated with a Likert scale ranging from 1 (extremely satisfied) to 9 (slightly dissatisfied). A favorable response was considered from moderately satisfied to extremely satisfied.

Adverse events (AE) were assessed based on severity and resulting disability. AE were self-reported by patients and picked up at each visit and by phone call one week after treatments, at 3 and 9 months of follow-up.

AEs were classified according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.³⁰

Eligible participants completed self-reported questionnaires, which were collected before each visit.

The study's primary outcomes included assessing the VMV at baseline and 3 and 9 months after the laser or sham intervention. The secondary outcomes included measuring changes in vaginal pH and evaluating subjective symptoms using the mentioned questionnaires. Additionally, any adverse effects experienced by the participants were recorded throughout the study.

Ethics Statement

The present clinical trial was conducted in accordance with the Helsinki Declaration and approved by the local Ethics Committee 2019 (Ref. CEIM: 047/2019). It was registered in the Clinical Trial Registry (NCT03956563) in Reus, Spain. Participants gave written informed consent and could withdraw from the study at any time.

Due to the COVID-19 pandemic, the study protocol was temporarily interrupted. An amendment was submitted to the local ethics committee and approved on May 28, 2020. Participants gave written informed consent and could withdraw from the study at any time.

Statistical Analysis

The final sample size in our study was 31 subjects. Accepting an alpha risk of 0.05 and a beta risk of less than 0.2 in a bilateral contrast, 14 subjects in each group are required to detect a difference equal to or greater than 9% in the vaginal atrophy value. The estimated common standard deviation is 8.³¹ A follow-up loss rate of 10% has been estimated.

The parametricity of the variables was examined, and logarithmic transformation of the variables was performed if required. ANOVA or Mann Whitney test, was used to assess differences between baseline characteristics among both Intervention groups. A General Linear Model assessed intra-intervention differences. An ANCOVA model adjusted by age was applied to evaluate differences between interventions. The Chi-square test evaluated differences in Patient Global Impression of Improvement. Statistical significance was defined as a *P* value of ≤ 0.050 for a 2-sided test. We performed analyses by using SPSS for Windows, version 21 (IBM corp., Armonk, NY, USA).

Results

56 women with GSM were screened for inclusion in the study; 27 participants finally completed the 3 and 9-month follow-up: 14 in the laser group and 13 in the sham group [Figure 1](#).

Potential confounders such as age at the time of the study, weight, age of menopause, and failure of first- and second-line treatments were comparable between the groups, with no significant differences observed at baseline, except for pH ($P=0.067$), as shown in [Table 1](#). However, this did not impact the final results.

At 3 months post-intervention, a significant improvement in VMV was observed in the laser group from (34.5 ± 3.6 to 44.5 ± 4.4), compared to the sham group from (30.7 ± 4.7 to 27.7 ± 6.3). The mean difference (mean $\pm$ 95% CI) was 12.4% (1.1; 24); $P < 0.033$ as shown in [Figure 2](#). Additionally, at 3 months, the proportion of patients with VMV improvement from baseline was significantly higher in the laser group ($P=0.004$): 12/14 patients (85.7%) compared to 4/13 patients (30.8%) in the sham group ($P=0.004$).

At 3 months post-intervention, 57.1% (8/14) of patients in the laser group and 23.1% (3/13) in the sham group achieved moderate estrogenization of VMV. However, the difference was not statistically significant ($P=0.072$). At 9 months post-intervention, VMV values and the percentage of patients with improvement returned to baseline as presented in [Figure 3](#).

Vaginal pH did not show significant differences at any of the evaluated time points.

Regarding GSM symptoms, the evaluation for dyspareunia was only possible in sexually active patients (22 out of 27).

At 9 months, the laser group showed a significant reduction in dyspareunia compared to the sham group, with a decrease of -2.59 ($P=0.049$). At both 3 and 9 months, dyspareunia significantly decreased following the laser intervention compared to their baseline ($P=0.001$) and ($P=0.007$), respectively as detailed in [Figure 4](#).

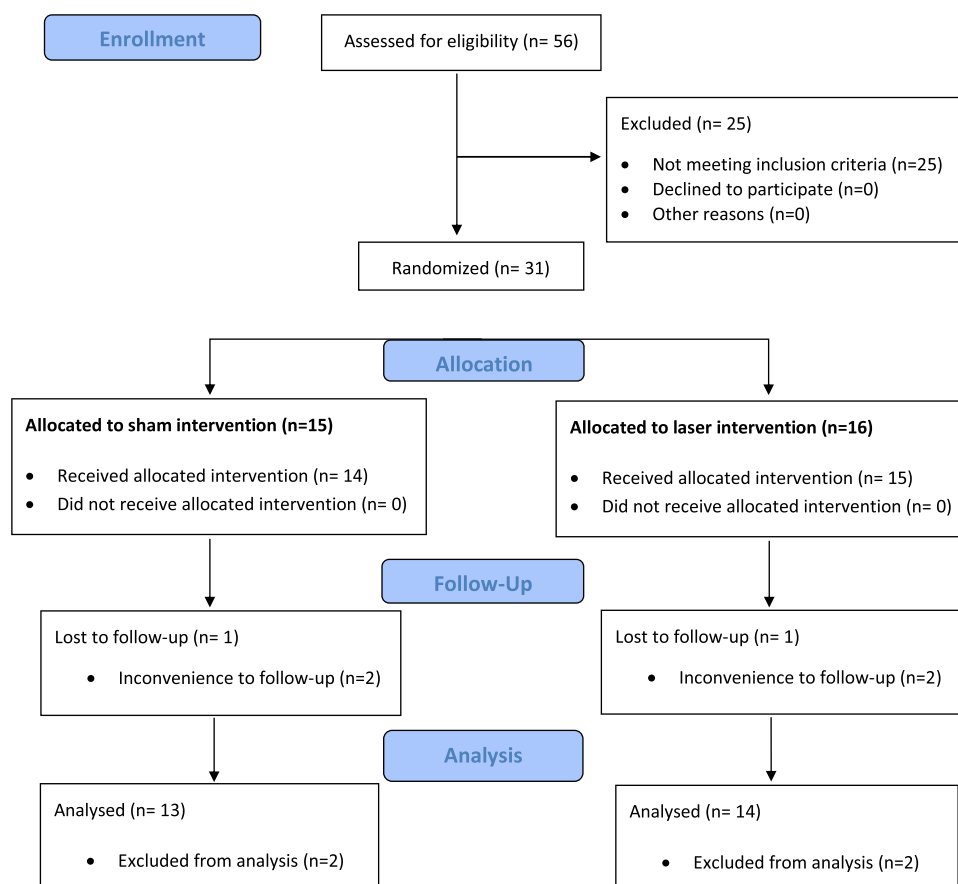


Figure 1 Flow chart of the enrollment of study participants.

Table 1 Baseline Characteristics of Participants

	Laser Group (n =14)	Sham Group (n =13)	P
Age, y	57.6 ± 4.25	58.3 ± 4.13	0.653
Age of menopause, y	48.5 ± 6.10	50.5 ± 3.97	0.317
Weight, kg	69.5 ± 9.36	65.8 ± 8.60	0.292
Body mass index, kg/m ²	26.8 ± 3.83	25.1 ± 3.06	0.219
Vaginal Maturation Value, %	34.5 ± 13.6	30.7 ± 16.9	0.529
Vaginal pH, U	6.29 ± 0.61	6.69 ± 0.48	0.067
Visual Analogue Scale (VAS)			
Dryness	6.00 ± 3.21	6.00 ± 2.34	1.00
Itching ^a	3.0 (0.97–5.5)	3.0 (0.00–6.0)	0.470
Dyspareunia ^b	7.69 ± 1.97	6.75 ± 2.80	0.338
Dysuria ^a	4.5 (0.75–7.0)	2.0 (0.50–5.5)	0.583
Burning	4.86 ± 3.48	4.69 ± 3.09	0.898

Notes: Data expressed as mean ± standard deviation, ^amedian (25th–75th percentiles). P for ANOVA or Mann Whitney test. Significant results in bold and borderline ones in *italic bold*.

Abbreviation: VAS, Visual Analogue Scale.

No differences were observed between the groups for other symptoms. However, the laser group showed significant improvements from baseline at 3 and 9 months in vaginal dryness, dysuria, and vaginal burning, as well as in vaginal pruritus at 9 months. In the sham group, significant improvements from baseline were observed in dysuria and vaginal burning as shown in Table 2.

The first treatment of the laser group reported mild but greater pain than the sham group ($p=0.029$). However, no differences in pain perception between the groups were observed during the following two treatments.

At 3 months post-intervention, PGI scores for GSM symptoms showed significantly greater improvement in the laser group compared to the sham group ($P=0.030$). All patients (100%) in the laser group rated their improvement as “better”, “much better”, or “very much better”, compared to 53.8% in the placebo group, as shown in Figure 5.

Similarly, at 3 months, the PGS questionnaire was rated as “extremely satisfied”, “very satisfied”, or “moderately satisfied” by 85.8% of patients in the laser group, compared to 46.2% in the sham group, showing a significant trend

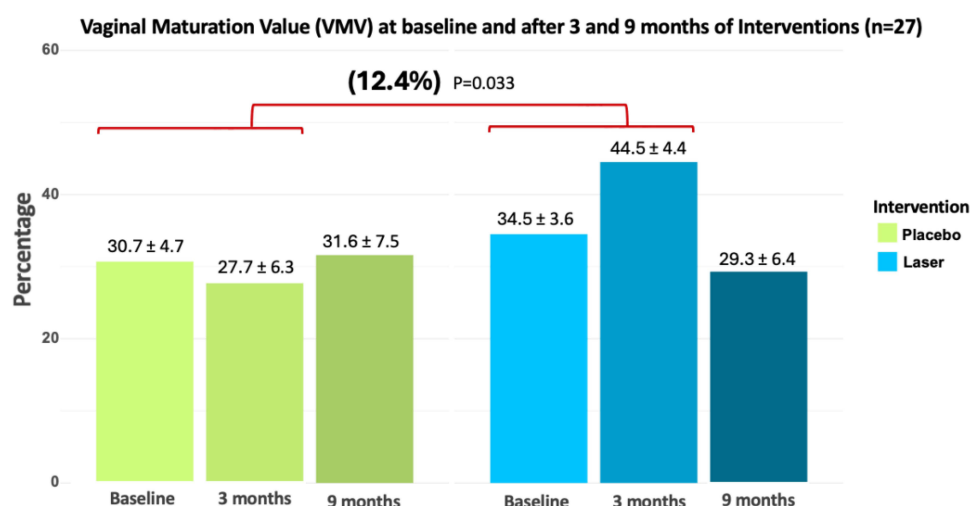


Figure 2 Graphical representation of the significant improvement in VMV observed at 3 months in the laser group compared to the sham group. The mean difference (mean ± 95% CI) was 12.4% (1.1; 24); $P < 0.033$.

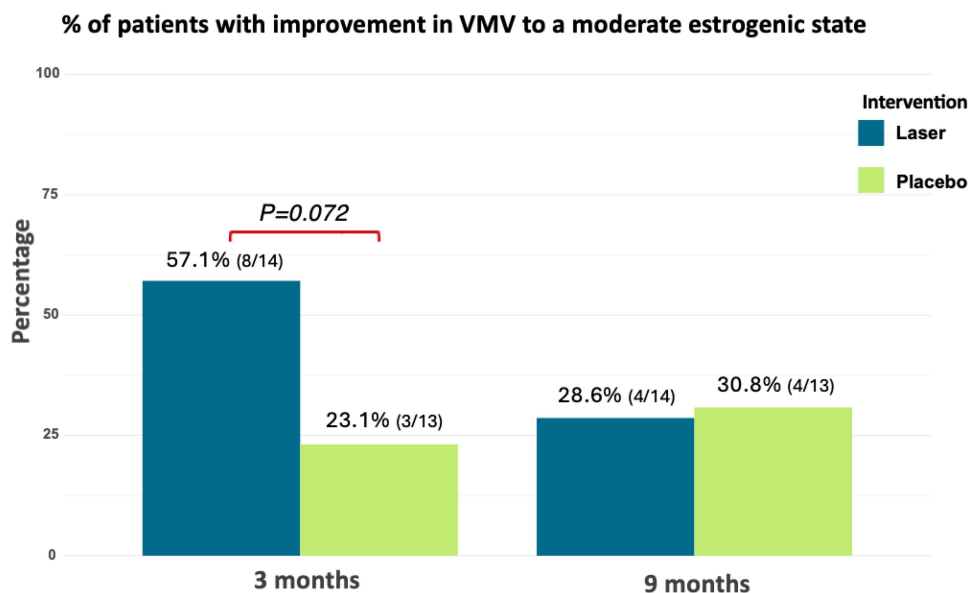


Figure 3 The histogram illustrates the proportion of patients achieving moderate estrogenization of VMV at 3 months post-intervention: 57.1% (8/14) in the laser group and 23.1% (3/13) in the sham group, indicating a trend toward significance ($P = 0.072$).

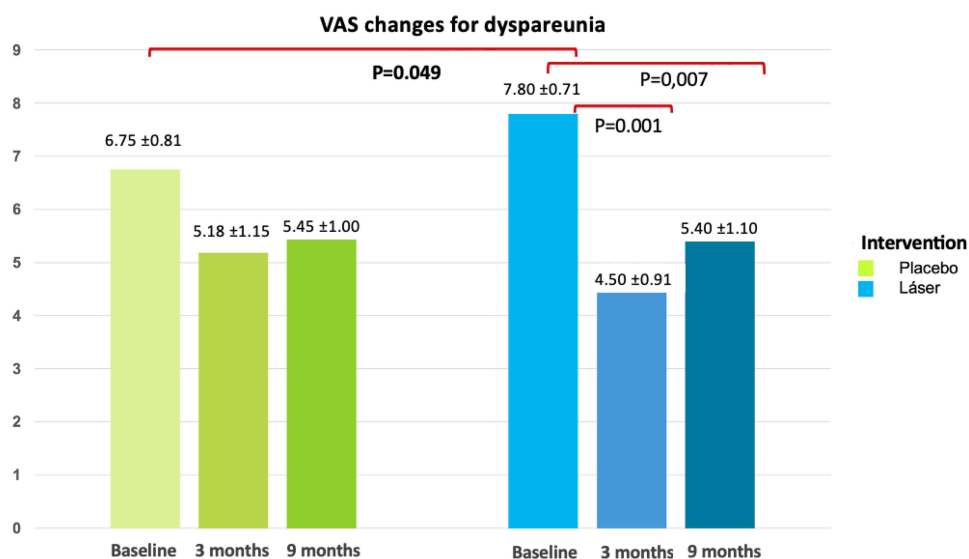


Figure 4 Graphical representation shows a significant reduction in dyspareunia in the laser group compared to sham at 9 months ($P = 0.049$). Dyspareunia also significantly decreased from baseline at 3 months ($P = 0.001$) and 9 months ($P = 0.007$).

($p=0.068$). At 9 months, 43% of the laser group and 23% of the sham group reported satisfaction, reaching marginal significance ($p=0.051$) as illustrated in Figure 6.

All participants successfully completed the study protocol, and mild AEs were observed in both groups.

The most frequently reported AEs included increased vaginal discharge, a sensation of warmth, mild to moderate pain lasting up to a maximum of 72 hours, introital irritation, mild vaginal edema, mild discomfort during urination, light bleeding, vaginal burning, and vaginal infection. These AEs were not observed at the 3- and 9-month follow-ups.

Discussion

This prospective, single-blind, randomized, parallel placebo-controlled trial demonstrated a significant overall mean increase of 12.4% in VMV at 3 months following the mixed laser intervention compared to the sham group. A global

Table 2 Changes in Visual Analogue Scale (VAS) Throughout the Study for All Population (n=27)

	Intervention Phase				Follow-Up Phase				Change Between Interventions Laser Group versus Sham Group			
Variable	Baseline	Post-T1	Post-T2	P for trend	3 months	P for trend	9 months	P for trend	At Post-T1	At Post-T2	At 3 months	At 9 months
Vaginal dryness												
Laser group (n=14)	6.00 ± 0.85	5.64 ± 0.71	4.36 ± 0.67	0.126	3.43 ± 0.69*	0.020^a	4.43 ± 0.91	0.021^a				
Sham group (n=13)	6.00 ± 0.65	6.23 ± 0.73	5.00 ± 0.83 ^a	0.282	4.50 ± 1.04	0.051^a	5.83 ± 0.70	0.253	−0.590 (−2.6; 1.6) P=0.586	−0.423 (−3.3; 2.5) P= 0.768	−0.680 (−3.6;2.2) P=0.634	−0.884 (−3.7;1.9) P=0.524
Vaginal itching												
Laser group (n=14)	3.49 ± 0.70	3.36 ± 0.52	2.64 ± 0.63	0.329	2.57 ± 0.78	0.314	1.21 ± 0.50[†]	0.008^a				
Sham group (n=13)	3.38 ± 0.87	2.69 ± 0.79	2.75 ± 0.73 ^a	0.466	2.25 ± 0.74	0.246	2.50 ± 0.53	0.219	0.644 (−0.96; 2.2) P=0.414	−3.03 (−2.7;−2.1) P= 0.801	0.401 (−2.2;−3.0) P=0.757	−1.28 (−3.1;−0.86) P=0.254
Dyspareunia												
Laser group (n=10)	7.80 ± 0.71	6.5 ± 0.98*	5.60 ± 0.86[†]	0.003^a	4.50 ± 0.91*	0.001^a	5.40 ± 1.10*	0.007^a				
Sham group (n=12)	6.75 ± 0.81	6.25 ± 1.09	5.50 ± 1.02	0.221	5.18 ± 1.15	0.148	5.45 ± 1.00	0.127	−0.600 (−4.3; 1.2) P=0.487	−1.67 (4.3;0.95) P=0.199	−2.20 (−4.5;0.86) P=0.058	−2.59 (−4.6;−0.004) P=0.049
Dysuria												
Laser group (n=14)	3.86 ± 0.73	2.71 ± 0.63	2.00 ± 0.60*	0.029^a	1.79 ± 0.57	0.021^a	0.79 ± 0.45*	0.001^a				
Sham group (n=13)	3.15 ± 0.77	2.00 ± 0.59	3.00 ± 0.80 ^a	0.172	1.61 ± 0.57	0.220	1.00 ± 0.44[†]	0.008^a	−0.045 (−2.0; 1.9) P=0.963	−1.58 (−4.6; 1.4) P=0.283	−0.604 (−3.2; 1.9) P=0.630	−0.815 (−2.8; 1.2) P=0.406
Vaginal burning												
Laser group (n=14)	4.86 ± 0.93	3.50 ± 0.71*	3.15 ± 0.67*	0.038^a	2.36 ± 0.63*	0.017^a	2.08 ± 0.73[†]	0.004^a				
Sham group (n=13)	4.69 ± 0.86	4.69 ± 0.82	4.25 ± 0.85	0.508	3.54 ± 0.82	0.227	2.92 ± 0.67*	0.015^a	−1.32 (−3.4; 0.78) P=0.207	−1.02 (−4.1; 2.0) P=0.497	−1.27 (−4.0; 1.5) P=0.353	−0.856 (−3.0; 1.3) P=0.417

Notes: Post-T1, after treatment 1 (Day 31); Post-T2, after treatment 2 (Day 61). VAS, Visual Analogue Scale: 0–10. Data expressed as mean ± standard error or mean (95% Confidence Interval, CI). Intra-intervention changes are analyzed by a General Linear Model. P for trend from baseline, ^alinear trend. *P < 0.05, ^{†</}

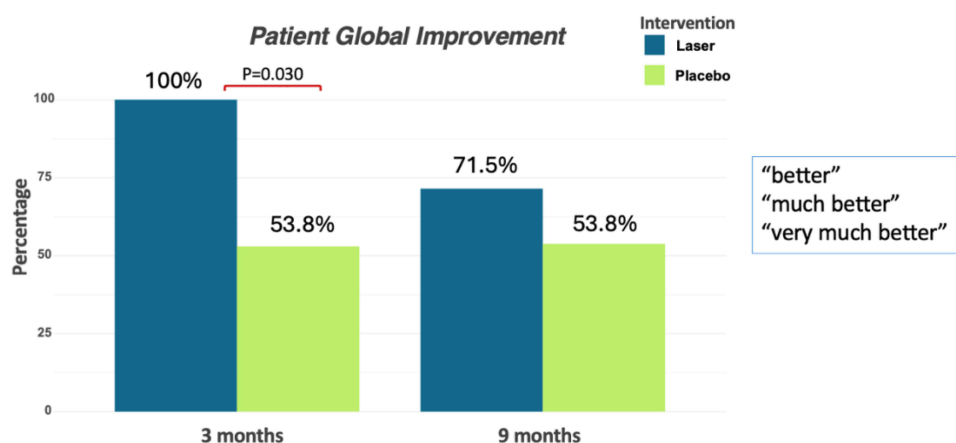


Figure 5 At 3 months, PGI scores for GSM symptoms showed significantly greater improvement in the laser group compared to the sham group ($P = 0.030$). All patients in the laser group rated their improvement as “better”, “much better”, or “very much better”, compared to 53.8% in the placebo group.

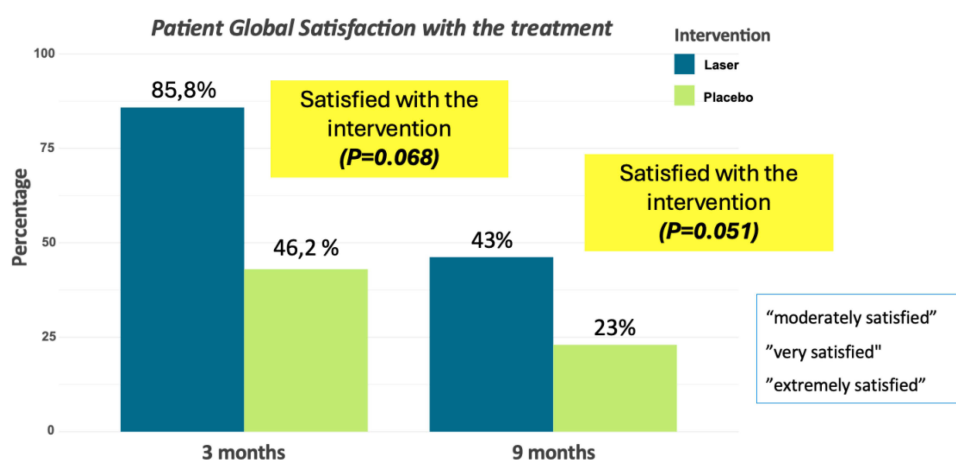


Figure 6 At 3 months, 85.8% of the laser group reported being “extremely”, “very”, or “moderately satisfied” with their treatment, compared to 46.2% in the sham group ($P = 0.068$). At 9 months, satisfaction was reported by 43% of the laser group and 23% in the sham group ($P = 0.051$).

improvement in VMV was observed in 85.7% (12/14) of patients in the laser group. Among these, 57.1% (8/14) achieved a moderate estrogenization score (50–64% estrogenic state), compared to the sham group, where 30.8% (4/13) of patients showed improvement, and only 23.1% (3/13) achieved moderate estrogenization. However, VMV returned to baseline levels at the 9-month follow-up.

The predominance of the non-ablative 1540 nm over the 10,600 nm laser allows for a more gradual response and more profound coagulation effect, enabling a reduction in the power of the 10,600 nm laser from 20–40W to 5W. This aligns with the experience in dermatology, where non-ablative lasers are known to be less aggressive and safer but less efficient than ablative counterparts, often necessitating additional treatment sessions based on patient progress.³² This is also consistent with Athanasiou’s findings which reported better results after 4 to 5 laser sessions.³³

According to our knowledge, few laser studies have employed VMV to assess the evolution of VA, with follow-up periods ranging from 1 to 6 months and yielding conflicting results.

Four prospective studies have reported significant improvements in VMV or Vaginal Maturation Index (VMI) with the 10,600 nm laser,^{33–36} while another prospective study found no significant changes.³⁷ Among the randomized trials, Cruz et al, in a three-arm study comparing 10,600 nm laser, vaginal estrogen (VE), and laser + VE, observed VMV improvement in all three groups at 8 weeks; however, at 3 months, improvement was noted only in the laser group compared to baseline.²⁹ Politano et al compared 10,600 nm laser, VE, and a moisturizer, finding improvement in

the VMI in the laser group at a 6-week follow-up.³⁸ Conversely, Paraiso et al, in a study comparing 10,600 nm laser and VE, reported no additional benefit from 10,600 nm laser.³⁹

The clinical increase in VMV observed in our study at 3 months with the mixed laser demonstrated a beneficial effect on the perceived severity of GSM. All patients (100%) in the laser-treated group reported feeling “better”, “much better”, or “very much better”, in contrast to only 53% of patients in the sham group. Two published RCTs, one comparing 10,600 nm laser with placebo⁴⁰ and another comparing 10,600 nm laser with VE,³⁹ found no differences in the perception of improvement between groups. However, other prospective studies have found improvements in patients following 10,600 nm laser treatment.^{41,42}

A meta-analysis revealed that 67.7% of the treatment effect for female sexual dysfunction is attributable to the placebo effect, suggesting that current treatments are only marginally more effective than placebo.⁴³ In our study, dyspareunia was the only symptom significantly improved in the laser group compared to the sham at 9 months. Other symptoms, including vaginal dryness, dysuria, and vaginal burning, showed significant improvement from baseline at 3 and 9 months, while vaginal pruritus improved at 9 months. The sham group showed statistically significant improvements only in dysuria and vaginal burning at 9 months compared to its baseline, further highlighting the positive outcomes achieved with mixed laser treatment.

Previous studies using 10,600 nm laser and VAS questionnaires for GSM symptoms have reported opposite results. While four RCTs with 10,600 nm laser found no significant differences in VAS scores between treatment groups,^{39,40,44,45} another three RCTs documented improvements in VAS scores.^{29,46,47}

In contrast, with vaginal estrogen therapy, symptoms of GSM frequently reappear within three months after stopping treatment and may even worsen. Additionally, maintaining long-term adherence to VE therapy remains a challenge.⁴⁸

Patient satisfaction was high. At 3 months, 85.8% of the laser group reported being “very satisfied” or “moderately satisfied”, compared to 46.2% in the placebo group. At 9 months, satisfaction in the laser group remained twice as high as in the sham group.

In line with our findings, two prospective observational studies indicated improved satisfaction levels with 10,600 nm laser treatment at 3 months.^{41,42} Similarly, Di Donato et al reported increased satisfaction rates with the 10,600 nm laser at 6 months.⁴⁹ However, one RCT comparing 10,600 nm laser with VE found that patients were equally satisfied with both treatments.³⁹

Regarding vaginal pH, no significant difference was observed between the two groups, suggesting that the mixed laser with the parameters used, does not alter the variables influencing vaginal pH. However, although pH improvement is a marker of vaginal health and bacterial balance, it is just one of several factors contributing to the improvement of GSM, such as increased vascularization and remodeling of the extracellular matrix.⁵⁰

Many non-randomized trials have reported a desirable decrease in vaginal pH to <5 following 10,600 nm laser treatment.^{34,51–53} Two studies with Er:YAG laser,^{54,55} and one with a non-ablative laser also demonstrated similar results.⁵⁶ However, the only RCT conducted in breast cancer patients treated with 10,600 nm laser did not observe any change in vaginal pH⁵⁷ and other non-randomized studies have shown a trend towards normalization, but without achieving pH<5.^{51,58}

In terms of safety, the AE in both the laser and sham groups were mild, brief, and self-limiting within 72 hours. Patients in both groups reported only mild pain during the intervention, mainly associated with the insertion of the vaginal probe into a previously dried, atrophic vagina. However, the laser power did not need to be reduced to complete the treatment. The decreasing pain observed in subsequent laser treatments may be attributed to improved vaginal trophism. There were no statistically significant differences in safety outcomes between the groups, and the laser treatment was well tolerated. These findings are consistent with previous research on the safety profile of 10,600 nm laser treatment⁴⁹ and with outcomes reported in 10 other RCTs.⁵⁹

Our study has several strengths. Firstly, to our knowledge, this was the first RCT with a mixed-wavelength laser specifically intended for women with GSM, demonstrating an increase in VMV with mild AE. Only one published study by Mezzana et al investigated the same mixed laser evaluating female sexual function and urinary incontinence.²⁴ The results reported significant improvement in the Female Sexual Function Index total score, sexual life satisfaction, and reduced urinary incontinence, with minimal AE. However, the author did not assess objective tests.

Secondly, the comparable pain reported by participants in both the laser and sham groups ensured that the treatment could be administered without compromising the blinding of the study. This finding also highlights the excellent tolerability of this mixed laser technology, even in individuals with severe vaginal atrophy.

Thirdly, using objective variables, such as VMV, effectively demonstrated the efficacy of the mixed laser in treating GSM.

Fourthly, all questionnaires (VAS scores, PGI, and PGS) were validated and independently completed by patients, thereby minimizing potential bias or influence from investigators.

But, we acknowledge the limitations of our study. Firstly, the small sample size may have increased the risk of a type II error (false negative), potentially limiting the ability to achieve greater statistical significance across all evaluated parameters. Although we initially intended to conduct a mid-study analysis and increase the number of participants, these plans were disrupted by the outbreak of the COVID-19 pandemic.

Secondly, the omission of the vaginal introitus from the treatment protocol may have influenced outcomes, particularly in addressing superficial dyspareunia, a condition often linked to loss of elasticity in this area during menopause.⁶⁰ This decision aimed to minimize potential discomfort and maintain the study's blind, as the introitus is highly sensitive and could react adversely to heat without anesthesia. However, excluding this region might have limited the treatment's overall effectiveness in alleviating superficial dyspareunia.

Third, the study coincided with the outbreak of the COVID pandemic, and we are unaware of the potential psychological and physical effects it may have had on the group of patients under study and how it could have influenced the final outcome.

Conclusion

The sequential application of the non-ablative 1540 nm wavelength, followed by the ablative 10,600 nm wavelength, has enabled a six- to eightfold reduction in 10,600 nm laser power compared to previously published data, enhancing its safety profile while achieving promising outcomes in GSM. The mixed laser emerges as a safe, well-tolerated, and effective alternative for treating GSM in patients unresponsive to conventional therapies, although the laser's long-term effects remain uncertain.

Further studies with an extended larger sample size, different laser settings, and extended follow-up periods are warranted to evaluate the long-term efficacy and side effects of the mixed 10,600 nm + 1540 nm laser for vaginal treatment of GSM.

Abbreviations

AE, Adverse events; BC, Breast cancer; GSM, Genitourinary Syndrome of Menopause; PGI, Patient's Global Impression of Improvement; PGS, Patients' Global Satisfaction; RCT, Randomized control trial; VA, Vaginal atrophy; VAS: Visual analog scale; VMI, Vaginal Maturation Index; VMV, Vaginal Maturation Value.

Data Sharing Statement

The authors confirm that individual deidentified participant data will not be shared publicly due to privacy and ethical restrictions. However, specific data sets and supporting study documents, such as the study protocol or statistical analysis plan, may be shared upon reasonable request. These requests should be directed to the main investigator at juanraul.salinas@salutsantjoan.cat. The data will be available for sharing starting six months after publication of the manuscript and will remain accessible for a period of one year.

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Disclosure

Juan Salinas Peña has had financial relations (expert testimonies and lectures) with QUANTA SYSTEM. The other authors report no potential conflicts of interest in this work.

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