

ORIGINAL STUDY

Treatment for vaginal atrophy using microablative fractional CO₂ laser: a randomized double-blinded sham-controlled trial

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Abstract

Objective: The aim of this study was to evaluate the efficacy of vaginal CO₂ laser for the treatment of vaginal atrophy compared to the sham procedure.

Methods: Between June 2016 and May 2017, postmenopausal women with moderate to severe intensity of any vaginal atrophy symptoms (VAS) were invited to participate in the study. A total of 88 women were randomized to receive treatment with either vaginal CO₂ laser or sham procedures every 4 weeks for three sessions. Both the participants and the evaluators were blinded to the treatment. Vaginal Health Index (VHI) score (primary outcome), VAS score, and the item for vaginal dryness from the International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms questionnaire were compared between the two groups by intention-to-treat analysis at 12 weeks after treatment.

Results: Eighty-eight women were enrolled into the study and nine women were lost to follow-up. After 12 weeks of laser treatment, the VHI, VAS, and International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms (item for vaginal dryness) scores were significantly improved. For VHI and VAS scores the mean difference between the laser group versus the sham group was 1.37 (95% CI: 0.12-2.63), $P < 0.001$ and -1.52 (95% CI: -2.21 to -0.82), $P = 0.03$, respectively.

Conclusions: This study demonstrated that the application of microablative fractional CO₂ laser was effective in treating vaginal atrophy. It could be a promising alternative treatment for postmenopausal women with vaginal atrophy.

Key Words: Fractional carbon dioxide laser – Genitourinary syndrome of menopause – Vaginal atrophy – Vaginal laser.

Video Summary: <http://links.lww.com/MENO/A582>.

Vulvovaginal atrophy or atrophic vaginitis refers to a group of postmenopausal symptoms related to an alteration of the vulva, vagina, and lower urinary tract. The International Society for the Study of Women's Sexual Health and The North American Menopause Society

proposed the nomenclature, “genitourinary syndrome of menopause” as a new terminology. These symptoms are associated with the decrement of estrogen after menopause.¹ The low levels of circulating estrogen produce a wide variety of anatomic, physiologic, and clinical changes in the urogenital area.² Clinical symptoms include vaginal dryness, irritation, soreness, dyspareunia, dysuria, and vaginal discharge. On examination, thinning, dryness, and pallor of the vaginal mucosa and flatten labia majora owing to loss of labial fat pad are common findings. As atrophy progresses, petechial hemorrhage may be found in the mucosa causing the vagina to become short and narrow.¹⁻³ Almost half of the postmenopausal women were reported to have vaginal atrophy.^{1,4,5} This percentage may, however, actually be underestimated due to underreporting by the patients or underrecognized by the healthcare providers. Evidence suggested that vaginal atrophy has profound negative effects on sexual health and quality of life.^{4,5} Hence, it is important to treat postmenopausal women with vaginal atrophy.

The treatment regimens, according to the 2013 position statement of The North American Menopause Society on

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management of symptomatic vulvovaginal atrophy, are non-prescription therapies; lubricants, moisturizers, herbal dietary supplements (eg, black cohosh, soy, or other herbs), and prescription therapies; vaginal estrogen, which is the criterion standard for treating vaginal atrophy.⁵ Selecting the treatment for vaginal atrophy depends on several factors such as severity of the condition, patient preference, effectiveness, and safety of the treatment. Ospemifene, which is a Selective Estrogen Receptor Modulator, is the other treatment option for moderate to severe dyspareunia associated with vaginal atrophy.⁵⁻⁹ In recent years, microablative fractional CO₂ laser has become available for treating pelvic floor dysfunction including vaginal atrophy. It showed a regenerative property with significant histological changes in cellular and connective tissue components.^{10,11} Several prospective studies reported significant improvement of signs and symptoms of vaginal atrophy including health-related quality of life after being treated with vaginal CO₂ laser. There were three case series that reported on the long-term positive effect of vaginal laser on vaginal atrophy symptoms (VAS; burning, dryness, and dyspareunia), Vaginal Health Index (VHI), and Female Sexual Function Index score for at least 1 year after three sessions of fractional CO₂ laser.¹²⁻¹⁴ Up to now, there are only a few studies reporting on the efficacy and safety of microablative fractional CO₂ laser by comparing it to the criterion standard therapy such as vaginal estrogen.¹⁵ But there is no report comparing vaginal laser with placebo or sham procedure. As a result, we conducted a randomized controlled trial to evaluate the efficacy of microablative fractional CO₂ laser by comparing it to a placebo (sham) procedure for the treatment of vaginal atrophy in postmenopausal women.

METHODS

From June 2016 to May 2017, a prospective randomized controlled trial was conducted at the Gynecology Clinic, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. This study was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University on March 31, 2016 (COA No. 276/2016). The study was registered in the Thai Clinical Trial Registry (No. TCTR20160627002).

Participants

Postmenopausal women (aged at least 50 years and had their last menstruation at least 1 year ago) with any VAS (moderate to severe intensity) were invited to participate in the study. Details of the study protocol, nature of the randomized trial, benefit, and risk of participating in the study were provided to the participants before enrollment. Written informed consent was obtained from all participants before enrollment. Women who had any history of hormonal therapy within the past 6 months, vaginal moisturizer or lubricant applications within the past 30 days, acute/recurrent urinary tract infection, or active genital infection were excluded from the study. In addition, if the participant was found to have a genital hiatus diameter of less than 2 cm (smaller than the vaginal probe size) or have pelvic organ prolapse stage 2 or

higher according to pelvic organ prolapse quantification system classification,¹⁶ they were also excluded.

Study protocol

Participants were randomized to either the laser group or the sham group (1:1 ratio). Simple randomization was generated by the computer. Allocation concealment of the generated codes was kept in opaque, sealed envelopes. The envelopes were opened by a research assistant at the first visit before initiating treatment. Demographic data and detailed medical history of all participants were collected including age, age at menopause, parity, type of delivery, history of vaginal reconstructive surgery, history of hormonal treatment, and sexual activity status. All participants were scheduled for four visits (V1, V2, V3, and V4) with a 4-week interval.

At each visit (V1, V2, V3, and V4), the participants were interviewed to assess the intensity of VAS using the VAS score.¹⁷ Signs of vaginal atrophy were evaluated during pelvic examination using a validated tool—VHI score¹⁸ by an investigator (S.B.) who was blinded to the participant's treatment. All participants were asked to answer item number 7 of the Thai-version International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms (ICIQ-VS) questionnaire¹⁹ to assess vaginal atrophy. After pelvic examination and completion of the questionnaire, the interventions were performed. The participants received the interventions in the first three visits (V1, V2, and V3). Laser or sham treatment was performed by an investigator (P.R.) who did not know the clinical outcomes of the treatment. In the last visit (V4), the study assessed the participants' satisfaction with the treatment and any adverse events they experienced during the study period.

Vaginal microablative fractional CO₂ laser treatment

The participants in the laser treatment group received the intervention by using the CO₂ laser machine (SmartXide² V²LR, DEKA, Florence, Italy). The laser settings were DEKA pulse mode, dot power 40 W, dwell time 1,000 ms, dot spacing 1,000 μm, and the smart stack parameter from 1 to 3. In the lithotomy position, the vaginal laser probe was inserted into the total length of the vagina and subsequently withdrawn 0.5 cm following each laser beam application until the distal end of the vaginal probe reached the introitus. The laser application was performed on an outpatient basis without local anesthesia. Participants were advised to avoid sexual intercourse or intravaginal devices for at least 3 days after the procedure owing to transient local inflammation at the vaginal mucosa generated by the laser application.

Sham procedure

Sham procedure was defined as a procedure mimicking the laser procedure without using the laser. Vaginal probe was inserted and withdrawn in the same manner as the laser treatment while the participants were in lithotomy position. Postprocedural recommendation was similar to the women who received the laser treatment.

Outcome measurements

The primary outcome was VHI score. The secondary outcomes were VAS score, score for the item for vaginal dryness (from ICIQ-VS questionnaire), participant's satisfaction with the procedures, and adverse events after the interventions. The outcome measurements were defined as follows.

Vaginal atrophy symptoms score

VAS score in this study was modified from Davila et al's study.¹⁷ We assessed four domains of VAS: dryness, irritation, soreness, and dyspareunia. The intensity of each domain was graded as none (0), mild (1), moderate (2), or severe (3). The total VAS score was calculated by the sum of these individual symptom scores divided by 4 for sexually active participants. For those participants who were not sexually active, the sum of individual symptom scores were divided by 3. Higher scores represent more severity of VAS.

Vaginal health index score

VHI score determines the severity of five signs of vaginal atrophy: elasticity, fluid volume, pH, epithelial integrity, and moisture. Each sign is rated from one to five. Summation of these scores represents the total VHI score which ranges from 5 to 25. High scores indicated less severity of vaginal atrophy.¹⁸

Vaginal dryness score of International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms questionnaire

ICIQ-VS questionnaire is a self-completed tool to assess the severity and impact of vaginal symptoms including vaginal atrophy. It has been translated and validated in the Thai language. The questionnaire consists of 14 items divided into 3 domains: vaginal symptoms, sexual matter, and quality of life. We chose item number 7 which provides information regarding vaginal dryness to assess for the symptom of vaginal atrophy.¹⁹

Adverse events

At the last visit (V4), all participants were asked about any adverse events after the interventions (eg, vaginal bleeding, discharge, vaginitis, pain after the procedure was done, and de novo dyspareunia).

Participant's satisfaction

At the last visit (V4), the participants were asked to answer a self-completed satisfaction questionnaire. The questionnaire used a five-point Likert scale (ie, very dissatisfied, dissatisfied, neutral, satisfied, and very satisfied) to assess the participant's satisfaction with the intervention.

Sample size calculation

The sample size calculation was based on the primary efficacy variable (VHI score), a 5% level of significance (two-sided), and a power of 80% were assumed. Previously, we conducted a pilot study so that the results obtained from

that study were used to calculate the sample size for this trial. Data from our pilot study showed mean \pm SD of VHI after 12 weeks of laser treatment was 20.5 ± 4.5 and mean \pm SD of VHI after 12 weeks of no laser treatment was 18 ± 2.8 . With 1:1 ratio, a sample size of 44 women per group was required taking into account a 20% dropout rate.

Statistical analysis

For baseline characteristics, categorical data were presented as number and percentage. Continuous data were presented as mean and standard deviation or median and interquartile range as appropriate. Intention-to-treat (ITT) analysis was used for primary outcome. When comparing the outcomes between pretreatment and posttreatment, paired *t* test or Wilcoxon sign rank test was used for continuous data. To compare outcomes between groups, continuous data were analyzed using unpaired *t* test or Mann-Whitney *U* test and categorical data were analyzed using chi-square test.

When there were missing data for any baseline characteristic variables, those participants would be excluded from the analysis. When outcome variables were missing, multiple imputation was used by regressing the outcomes on the other observed data using a linear regression model because we assessed the outcomes at multiple time points. All data were analyzed using SPSS software version 22.0 (SPSS science, Chicago, IL) for Windows. *P* value less than 0.05 was considered statistically significant.

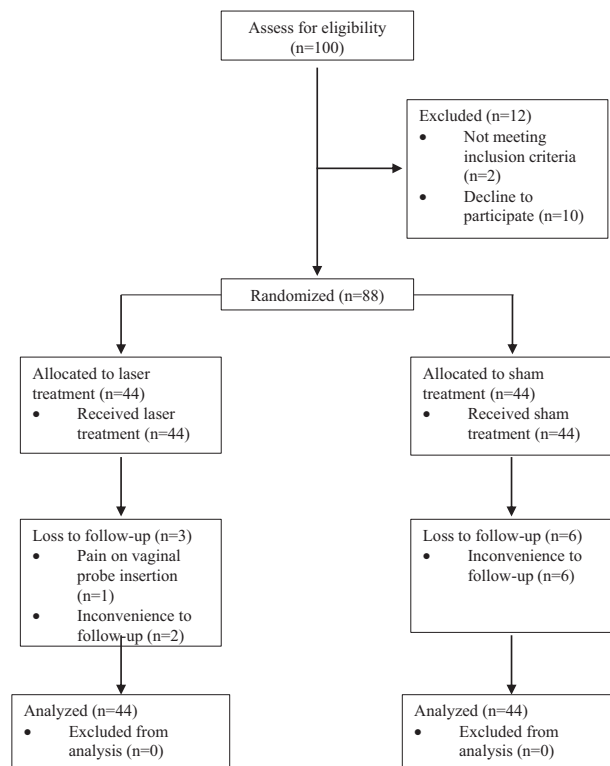


FIG. 1. CONSORT flowchart of participants.

TABLE 1. Demographic data

Characteristics	Total (Mean ± SD)	Laser group (n = 44) (Mean ± SD)	Sham group (n = 44) (Mean ± SD)
Age, y	60.78 ± 7.77	61.73 ± 8.01	59.84 ± 7.49
Age at menopause, y	49.21 ± 3.49	48.95 ± 3.04	49.47 ± 3.92
Number of children	2.16 ± 1.52	2.11 ± 1.51	2.20 ± 1.53
	N (%)	N (%)	N (%)
Normal labor	59 (67.05)	33 (75.00)	26 (59.10)
Cesarean section	28 (31.82)	10 (22.73)	18 (40.91)
History of vaginal reconstructive surgery	6 (6.82)	5 (11.36)	1 (2.27)
History of hormonal use	18 (20.45)	10 (22.73)	8 (18.18)
Active sexual lifestyle	34 (38.64)	10 (22.73)	24 (54.55)

Our statistical analysis plan did not include a plan for managing confounding variables on the primary outcome. Data from baseline characteristics demonstrated that sexually active lifestyle was different between the two groups. There is evidence that sexual function may relate to vaginal atrophy,²⁰⁻²² so we performed analysis of covariance to control the confounding effect of the sexually active variable.

RESULTS

A total of 88 participants were randomized. In the laser group (n = 44), three participants withdrew from the study. One participant withdrew from the study because she could not tolerate the pain when the vaginal probe was inserted into the vagina. The other two women withdrew from the study claiming that it was inconvenient for them to come according to the schedule of the study. In the sham group (n = 44), six participants were lost to follow-up because it was inconvenient for them to come in to receive the treatment. Because we planned to use the ITT analysis for this study, all 44 participants from each group were included for analysis (Fig. 1). Linear regression technique was used to impute those missing outcome data for the analysis. We had nine missing outcome data (three in the laser group and six in the sham group). The mean ± SD age of the enrolled women was 60.78 ± 7.77 years. The mean ± SD age at menopause was 49.21 ± 3.49 years. Thirty-four women

(38.64%) were sexually active (10 [22.73%] in the laser group and 24 [54.55%] in the sham group; Table 1).

Outcome measurements at baseline are shown in Table 2. In the laser group, the mean ± SD VHI and VAS scores were 14.18 ± 3.39 and 2.27 ± 0.42, respectively. In the sham group, the mean ± SD VHI and VAS scores were 14.66 ± 2.91 and 2.02 ± 0.40, respectively. At baseline, the VHI score (P = 0.48), VAS score (P = 0.06), and ICIQ-VS, the item for vaginal dryness (P = 0.09) were comparable between both groups (Table 2). Data were compared between baseline and 12-week follow-up (Table 2). In the laser group, there was significant improvement for all outcomes at week 12 when compared to baseline. The VHI score significantly increased from 14.18 ± 3.39 at baseline to 17.45 ± 2.61 at 12-week follow-up, P < 0.001. The VAS score decreased from 2.27 ± 0.42 to 1.83 ± 0.51, P < 0.001. As for ICIQ-VS, the item for vaginal dryness significantly decreased from 5.00 (2.00-6.00) to 3.24 (0-4.00), P = 0.02. In the sham group, there was no statistical difference of the VHI score at 12-week follow-up period (P = 0.06). The VAS score increased from 2.02 ± 0.40 at baseline to 2.06 ± 0.49 at 12-week follow-up (P = 0.59). The ICIQ-VS, the item for vaginal dryness decreased at week 12 (P = 0.07) (Table 2).

Because the outcomes at baseline were not significantly different between groups, we assumed that the outcomes at 12-week follow-up could represent the change after treatment.

TABLE 2. Vaginal signs and symptoms at baseline and 12 weeks after treatment

	Baseline	12 Weeks after treatment	P
VHI score (mean ± SD)			
Laser group (n = 44)	14.18 ± 3.39	17.45 ± 2.61	<0.001 ^a
Sham group (n = 44)	14.66 ± 2.91	16.08 ± 3.27	0.06 ^a
P value	0.48 ^b	<0.001 ^b	
VAS score (mean ± SD)			
Laser group (n = 44)	2.27 ± 0.42	1.83 ± 0.51	<0.001 ^a
Sham group (n = 44)	2.02 ± 0.40	2.06 ± 0.49	0.59 ^a
P value	0.06 ^b	0.03 ^b	
ICIQ-VS, vaginal dryness (median [IQR])			
Laser group (n = 44)	5.00 (2.00-6.00)	3.24 (0-4.00)	0.02 ^c
Sham group (n = 44)	4.00 (2.00-6.00)	2.00 (0.26-4.00)	0.07 ^c
P value	0.09 ^d	0.56 ^d	

P values of less than 0.05 were considered statistically significant.

ICIQ-VS, International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms; VAS, vaginal atrophy symptoms; VHI, Vaginal Health Index.

^aP value for paired t test.

^bP value for unpaired t test.

^cP value for Wilcoxon sign rank test.

^dP value for Mann Whitney U test.

TABLE 3. Comparison of the participants' satisfaction between the laser and sham groups

	Laser group (n = 39) N (%)	Sham group (n = 38) N (%)	P
Very satisfied or satisfied	31 (79.5%)	17 (44.7%)	0.002 ^a
Neither satisfied nor dissatisfied or lower	8 (20.5%)	21 (55.3%)	

^aP value for chi-square test.

When we compared the outcomes at 12-week follow-up with the ITT analysis, there was statistically significant differences between the two groups for VHI score ($P < 0.001$) and VAS score ($P = 0.03$) with the mean difference of 1.37 (95% CI: 0.12-2.63) and -0.23 (95% CI: -0.45 to -0.27), respectively. There was, however, no significant differences for ICIQ-VS, the item for vaginal dryness ($P = 0.56$) (Table 2). The results from per-protocol analysis were similar to the ITT analysis. A one-way analysis of covariance was conducted to determine whether there were any significant differences between the laser and sham groups for VHI score at 12-week follow-up after controlling for active sexual status. After the active sexual status was controlled, we saw a significant improvement in the VHI score in the laser group compared to the sham group ($F(1,86) = 6.47$, $P < 0.05$).

Seventy-seven women answered the satisfaction evaluation questionnaire (39 women from the laser group and 38 women from the sham group). The comparison of the participants' satisfaction from both groups is shown in Table 3. There was a significant difference between the two groups for "very satisfied or satisfied" and "neither satisfied nor dissatisfied or lower" ($P = 0.002$). Participants experiencing minor adverse events (ie, vaginal bleeding, vaginal discharge, vaginitis, and pain after procedure) are shown in Table 4. The adverse events were not statistically significant between the groups. One participant from the laser group was diagnosed with bacterial vaginosis 1 week after the procedure and was treated with oral metronidazole for 7 days.

DISCUSSION

Vaginal microablative fractional CO₂ laser for treatment of vaginal atrophy is the activation of vaginal tissue to regenerate. The supraphysiologic level of the heat from the laser induces production of a variety of growth factors, which induce cell proliferation and subsequent tissue repair.²³ Microscopic evaluation of the vaginal tissue after laser treatment showed thickening of the epithelial layer and increase papillae projecting from the connective tissue into the epithelium, which represent the regenerative characteristic of the vaginal mucosa that is similar to the premenopausal vaginal mucosa.^{10,11}

Our randomized trial showed that after 12 weeks of treatment with vaginal CO₂ laser, there were significant improvements in the VHI score and VAS score among women with vaginal atrophy, whereas in the sham group, there were no significant improvements for all measurements. These results were consistent with other previous uncontrolled prospective

studies that showed vaginal CO₂ laser treatment did improve symptoms and signs of vaginal atrophy.^{12-14,24-26} In a previous randomized-controlled trial conducted by Cruz et al,¹⁵ they evaluated the efficacy of fractional CO₂ laser and compared it to local estrogen and the combination of both treatments. Participants were randomly assigned to three treatment arms: laser with estriol treatment, laser with placebo treatment, and sham procedure with estriol treatment. After 20 weeks, the participants who received laser with estriol treatment and laser with placebo treatment showed significant improvement in VHI and VAS compared to the participants that were only treated with estriol. In another randomized trial, the effects of fractional CO₂ laser therapy were compared to vaginal promestriene and vaginal lubricants among women with genitourinary syndrome of menopause.²⁷ The women from the CO₂ laser group had a significantly higher VHI score after 14 weeks of treatment compared to women in the promestriene and lubricant groups. Vaginal maturation significantly improved in the CO₂ laser group compared to the other treatment groups, but it should be noted that they did not compare the results of the laser group to a sham group to confirm the efficacy of CO₂ laser versus placebo. Our study is the first trial that compared the effect of vaginal CO₂ laser with the placebo (sham procedure) to see whether the placebo effect can improve VAS. Our results confirmed that the CO₂ laser could improve VHI and VAS when compared to the sham group. After completion of the study, all participants were treated according to The North American Menopause Society guideline for vaginal atrophy among postmenopausal women.⁵ We detected minor adverse effects of the vaginal laser which were similar to previous reports.^{12,14,15,27} These side effects lasted only for a few days. No serious adverse event was noted in this study.

The strength of this study was its randomized trial design that compared the effects of vaginal CO₂ laser to the sham procedure. Also, the dropout rate in the study was small. In addition, this study was double blinded so bias was minimized. Moreover, we used the standardized outcome measurements (VHI and VAS scores) and validated questionnaire (ICIQ-VS, item for vaginal dryness) to assess vaginal atrophy. Furthermore, the vaginal laser and the sham procedures were performed by a single operator to avoid interpersonal clinical skill variation.

This study had some limitations. First, we did not study the effect of vaginal laser on sexual function²⁸ because sexual

TABLE 4. Comparison of the complications between the laser and the sham groups

	Laser group (n = 41) N (%)	Sham group (n = 38) N (%)	P
Vaginal bleeding	0 (0)	1 (0.26)	0.30 ^a
Vaginal discharge	3 (0.73)	1 (0.26)	0.34 ^a
Vaginitis	1 (0.24)	0 (0)	0.33 ^a
Pain after procedure	3 (0.73)	4 (1.05)	0.34 ^a
De novo dyspareunia	0 (0)	0 (0)	–

^aP value for chi-square test.

activity among Thai menopausal women was low (38%). Second, the follow-up period in this study was only 12 weeks. Thus, additional study with a longer follow-up period and larger sample size should be conducted to assess the long-term effects of vaginal CO₂ laser in terms of efficacy and side effects. Third, the sham procedure was performed in the same manner as the laser treatment but without laser power application. Participants might, however, perceive that there was no noise and vibration during the procedure. This might cause unblinding to those participants and result in bias to participants' reported outcomes. Fourth, we assessed adverse events at the last visit. This could be a source of recall bias because participants might not recall the discomfort which occurred in the previous visits.

CONCLUSIONS

Vaginal microablative fractional CO₂ laser was effective in treating women with vaginal atrophy compared to the sham procedure at week 12. Vaginal microablative fractional CO₂ laser could be an alternative treatment for postmenopausal women with vaginal atrophy.

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