Clobetasol Compared With Fractionated Carbon Dioxide Laser for Lichen Sclerosus

A Randomized Controlled Trial

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OBJECTIVE: To compare 6-month safety and efficacy outcomes of fractionated CO_2 laser (laser) with topical clobetasol propionate (steroid) for treatment of symptomatic vulvar lichen sclerosus.

See related editorial on page 965.

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© 2021 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. All rights reserved. ISSN: 0029-7844/21 **METHODS:** We conducted a single-center randomized controlled trial that compared fractionated CO_2 laser with steroid treatment for patients with biopsy-proven lichen sclerosus. Randomization was stratified by prior clobetasol propionate use. The primary outcome was mean change in Skindex-29 score at 6 months. A total sample size of 52 participants were recruited to detect a mean difference of 16 points on the Skindex-29 (SD±22) with 80% power, based on a one-sided two-sample *t* test with α =0.05, accounting for 10% attrition. Secondary outcomes included validated subjective and objective measures. Intention-to-treat, per protocol, and regression analysis based on prior steroid exposure were performed.

RESULTS: From October 2015 to July 2018, 202 women were screened, 52 were randomized, and 51 completed a 6-month follow-up. No significant difference was found in baseline demographics, symptoms, and physician assessment scores. There was greater improvement in the Skindex-29 score in the laser arm at 6-months (10.9 point effect size, 95% CI 3.42–18.41; P=.007). Overall, 89% (23/27) of patients in the laser group rated symptoms as being "better or much better" compared with 62% (13/24) of patients in the steroid group, P=.07. More patients (81%, 21/27) were "satisfied or very satisfied" with laser treatment compared with steroid treatment (41%, 9/24); P=.01. After stratification for previous steroid use, the significant change of Skindex-29 score was only seen in the previously exposed group. There was one adverse event in each group: minor burning and blistering at the laser site and reactivation of genital herpes 1 week after starting steroid. CONCLUSION: Fractionated CO₂ laser treatment showed significant improvement in subjective symptoms and objective measures compared with clobetasol propionate, without serious safety or adverse events at 6 months.

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ulvar lichen sclerosus is a dermatosis resulting in significant architectural changes to the labia minora, clitoris and anus including labial atrophy, hypopigmentation, synechiae, and introital narrowing. These skin changes often lead to itching, vulvar pain, and dyspareunia.¹ Lichen sclerosus is associated with an increased risk of vulvar squamous cell carcinoma with an incidence of about 3-9%.²⁻⁴ However, many patients are not adequately treated owing to inconsistent prescribing practices or patient intolerance. Evidence suggests that patients who have adequate treatment with resolution of symptoms, repigmentation, and return to normal skin texture have a decreased incidence of transformation to squamous cell carcinoma.^{2,4,5} Clobetasol propionate, a potent topical steroid, has long been considered the goldstandard treatment for vulvar lichen sclerosus and works through antiinflammatory, antimitotic, and immunosuppressive effects with a reported range of efficacy for symptomatic improvement of 66-96%,⁶⁻¹⁰ and complete remission of 23-54%.^{5,7,10}

The vulvovaginal SmartXide2– V^2 -LR laser system is a fractionated carbon dioxide (CO₂) laser with maximum 40 W power and laser energy emission at 10,600 nanometer wavelengths. Fractionated CO₂ laser treatments create small, 200-micron treatment spots on vulvar and vaginal skin hypothesized to create heat shock of proteins, damaging signaling cytokines and growth factors, which recruit fibroblasts and increase cell division. Histopathologic reports show stimulation of fibroblastic growth, biosynthesis of collagen, and restoration of the extracellular matrix with organized collagen fibers.^{11,12}

A few case series report the use of ablative CO_2 lasers for refractory vulvar lichen sclerosus, with mixed results.¹³⁻¹⁷ Three case series studies have reported the use of fractionated CO_2 laser in addition to topical clobetasol propionate for symptomatic lichen sclerosus, with improvement of symptoms in 80-88% of patients and no progression of disease.¹⁵⁻¹⁷ The only randomized controlled study, by Bizjak Ogrinc et al, reports symptomatic and clinical objective improvement of vulvar lichen sclerosus with neodymium:yttrium aluminum garnet laser adjuvant treatment to clobetasol propionate.¹⁸ Neodymium:yttrium aluminum garnet lasers have a wavelength of 1,320 nm, compared with CO_2 lasers, which have a wavelength of 10,600 nm. This 10-fold difference means that neodymium:yttrium aluminum garnet lasers penetrate to a depth of 3-4 mm, whereas CO_2 lasers target water within tissue with less thermal spread and decreased penetration at 0.5 mm.¹⁹ We sought to compare fractionated CO₂ laser treatment with clobetasol propionate treatment and observe safety. We hypothesized that it is an effective alternative treatment for patients with symptomatic vulvar lichen sclerosus.

METHODS

This study was a single-center, randomized controlled trial, approved by the Medstar Health Research Institute Institutional Review Board, to compare fractionated CO_2 laser (laser) to topical clobetasol propionate steroid treatment (steroid) for postmenopausal patients with lichen sclerosus. Patients were recruited from urogynecologic and gynecology academic medical center office visits with vulvar biopsy-proven lichen sclerosus. The inclusion criteria were postmenopausal, English-speaking women with significant symptoms based on Skindex-29 scores higher than 21, indicating at least mild bother. Participants were excluded with greater than stage 2 pelvic organ prolapse, prior vaginal mesh for prolapse, active genital infection, known vulvar malignancy, planning pregnancy, active or prior diagnosis of gynecologic malignancy, allergy to topical steroid, current treatment with systemic immunomodulators, intrauterine device in place, or prior pelvic radiation.

Fifty-two women were recruited to detect a mean difference of 16 points on the Skindex-29 (SD \pm 22 for both groups), 20-22 with 80% power between the study groups based on a one-sided two-sample t test with $\alpha = 0.05$, accounting for 10% attrition. The effect size of 16 points was selected because it equals the difference of two health-related quality of life (HRQOL) categories (severe, moderate, mild, very little) that we intended to represent a clinically meaningful difference. Patients underwent block randomization with a 1:1 ratio by an investigator not involved in enrollment process, with stratification for participants based on prior clobetasol use. Group allocation was kept in sealed sequentially numbered opaque envelopes. Owing to the nature of the treatment, blinding of participants or assessors was not possible; however, blinding was maintained for data analysis.

Patients completed an 8-week washout period before enrollment if they were currently using clobetasol propionate or other topical or systemic immunomodulator. Patients in the steroid arm were prescribed clobetasol propionate 0.05% ointment for topical use over the vulva and perianal area nightly for 1 month, three times weekly for 2 additional months, then as needed. Patients received phone call check-in 2 weeks after enrollment, an optional 3month follow-up office appointment and follow-up at 6 months for data collection.

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Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram.²³ Flowchart of trial participant enrollment, allocation, and follow-up characteristics. Study had a high retention rate at 6-month follow-up.

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Table 1. Baseline Socioeconomic Characteristics in Treatment Group Comparison

		Treatmo	ent Group
Variable	Total (n=52)	Laser (n=27)	Steroid (n=25)
Age (y)	64.5±10.4	67.6±11.0	61.5±8.9
Age of menopause (y)	47.3 ± 5.8	47.3±6.0	47.3 ± 5.8
BMI (kg/m ²)	28.66 ± 5.9	28.4 ± 6.6	28.9 ± 5.2
Median parity (IQR)	2 (2)	2 (2.75)	2 (1.5)
Education		. ,	× ,
High school or equivalent	7 (14)	4 (15)	3 (13)
Vocational	1 (2)	0 (0)	1 (4)
Associate degree	6 (12)	4 (15)	2 (8)
Bachelor's degree	14 (28)	4 (15)	10 (42)
Graduate or professional	22 (44)	14 (55)	8 (33)
Prior clobetasol use			- (/
Yes	25 (50)	14 (52)	11 (47)
No	25 (50)	13 (48)	12 (53)
Median duration of lichen sclerosus diagnosis (v) (IOR)	0.56 (3.84)	0.8 (4.92)	0.48 (2.84)
0–1	27 (54)	13 (52)	14 (56)
2-5	13 (26)	6 (24)	7 (28)
5 or more	10 (20)	6 (24)	4 (16)
Estrogen therapy	()	0 (2)	. ()
Yes	24 (46)	16 (59)	8 (32)
No	27 (52)	11 (41)	16 (64)
Unknown	1 (2)	0	1 (4)
Median duration of estrogen therapy (v) (IOR)	0.83 (1.75)	0.58 (2)	1.25 (0.88)
Employment			× ,
Unemployed	3 (6)	1 (4)	2 (8)
Full-time	20 (39)	8 (30)	12 (50)
Part-time	4 (8)	3 (10)	1 (4)
Retired	24 (47)	15 (56)	9 (38)
Marital status			- ()
Single	8 (16)	3 (11)	5 (21)
Divorced	5 (10)	3 (11)	2 (8)
Married	29 (58)	14 (54)	15 (63)
Widowed	8 (16)	6 (24)	2 (8)
Living situation	- ()		
Alone	11 (23)	6 (23)	5 (22)
Home, not alone	38 (77)	20 (77)	18 (78)
Assisted living or nursing home	0	0	0
Private insurance	40 (78)	22 (82)	18 (75)
State insurance	12 (24)	6 (22)	6 (25)
State insurance	12 (24)	6 (22)	6 (25)

BMI, body mass index; IQR, interquartile range.

Data are mean±SD or n (%) unless otherwise specified.

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Patients in the laser arm had a total of three office laser treatments 4–6 weeks apart, delayed by 2 weeks after vulvar biopsy, if not previously documented. The vulvovaginal SmartXide2-V2-LR laser system fractionated CO₂ laser was used. The laser was set at 26 W, dwell time 800 microseconds, DOT spacing at 800 micrometers and normal scan mode for baseline laser treatment. Two additional treatments at a minimum of four to a maximum of 6 weeks apart were performed with the following settings: power 30 W, dwell time 1,000 microseconds, spacing 1,000 micrometers at normal scan mode with smart pulse.²⁴ Visually affected areas of vulvar and perianal lichen sclerosus were treated with single pass, except for the glans of the clitoris and clitoral hood, which were spared with at least a 5 mm margin. Before laser treatment, eutectic local anesthetic (lidocaine 2.5%, prilocaine 2.5% topical ointment) was applied for 30 minutes then wiped off. Patients were provided an additional supply of eutectic local anesthetic for any discomfort after treatment. Patients did not receive any additional office visits outside of the treatment encounters.

Data collection was completed at baseline, 6 months, and 12 months with multiple validated scales, surveys, and photo documentation providing reproducible measures of vulvar symptoms and appearance as primary and secondary outcomes. Sociodemographic information was collected at baseline. The primary outcome was change in mean Skindex-29 score at 6 months, and the 6month outcomes are presented in this article. The Skindex-29 is a validated questionnaire for assessing acute dermatologic symptoms over a 4-week period with more negative scores indicating greater improvement.

Secondary outcomes of subjective symptoms included a validated visual analog scale (subjective VAS), the VSQ (Vulvovaginal Symptoms Questionnaire), Skindex-29 subscores, and the PGI-S (Patient Global Impression of Satisfaction) and PGI-I (Patient Global Impression of Improvement). Symptoms included vulvar itching, vulvar burning, vulvar irritation, pain with intercourse, tearing of the vulvar skin, painful urination, and painful defecation within the validated subjective VAS (scaled 0-10, higher values indicating increased symptoms). The VSQ is a validated measure of vulvar symptoms, emotions, life effect, and sexual effect in postmenopausal women; higher total score corresponds to lower quality of life.²⁵ Patient satisfaction and global impression of improvement were assessed

using a simple validated VAS from 0 to 5 ("much worse to much better").

Secondary objective measures of the clinical appearance of vulvar lichen sclerosus were completed by investigators at concurrent time points with the patient questionnaires: baseline and 6 months. Nonidentifiable photo documentation of vulvar appearance was collected. Investigators scored visual appearance, including white plaques or hypopigmentation, cigarette paper or thin skin, introital narrowing, perianal involvement (figure-ofeight shape), loss of labia minora, fusion of labia minora, phimosis of clitoral hood, vulvar fissure, and erosion, scaled on a validated VAS from 0 to 10; higher scores indicate worse appearance. Additionally, investigators completed the validated VHI (Vaginal Health Index), evaluating vulvovaginal overall elasticity, fluid secretion type and consistency, pH, epithelial mucosa, and moisture on a scale 1-5 from none to excellent, with lower values indicating decreased vaginal health.²⁶

Statistical intention-to-treat and per protocol analysis was completed in R, with demographic and questionnaire scores reported as means and SDs or medians and interquartile ranges. Chisquared or Fisher exact test, two-sample t test, and Mann–Whitney U test were used to compare categorical, continuous, and nonparametric variables, respectively. D-Agostino test was used to assess normality. A two-way analysis of variance analysis of mean Skindex-29 score improvement based on prior steroid exposure and treatment group was performed.

RESULTS

From October 2015 to July 2018, a total of 202 women were screened, 92 declined participation, and 58 were excluded, for a total enrollment of 52 participants. Twenty-seven women completed laser treatment and 6-month follow-up; none were lost to follow-up. Twenty-four patients completed steroid treatment and 6-month follow-up, with one dropout for inability to contact (Fig. 1).²³ At 6 months, 74% of patients reported complete compliance with treatment, one partial compliance, four without report, and one patient reported stopping treatment for lack of efficacy in the steroid group. No differences were found among socioeconomic factors between study groups (Table 1). No significant differences were present between groups for duration of lichen sclerosus diagnoses, duration of any prior clobetasol use in exposed group, history of estrogen therapy (oral or vaginal), or duration of estrogen treatment. There

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were no significant differences in patient baseline vulvovaginal symptoms on Skindex-29, VSQ, or subjective VAS scores between treatment groups, except vulvar tearing, and dyspareunia. There was no significant difference in baseline physician objective assessment of disease severity on VHI or objective VAS score, except for white plaques VAS score (Table 2). In addition, stratification groups were similar at baseline for all outcome measures, except phimosis score.

The primary outcome was the mean change in Skindex-29 scores between baseline and 6 months. In the intention-to-treat analysis, greater improvement was noted for laser group compared with the steroid group (laser -16.83 ± 18.09 vs steroid -5.92 ± 5.81 ; P=.007; Table 3). Similar results were seen in the per protocol analysis with laser (n=26) compared with steroid (n=19) (-16.46 ± 17.21 vs -5.79 ± 5.29 ; P=.007), with size effect -10.66 (95% CI -18.93 to -2.39).

A similar trend was seen for secondary Skindex-29 subscores including emotion (laser -19.63 ± 21.92

vs steroid -6.77 ± 9.9 ; P=.011) and symptoms (laser -21.03 ± 22.18 vs steroid -4.91 ± 11.19 ; P=.002); the function subscore was similar between groups (laser -10.65 ± 18.97 vs steroid -5.30 ± 8.64 ; P=.210; Fig. 2). After stratification for previous clobetasol propionate treatment, the statistically significant change of Skindex-29 overall score was only seen in the previously exposed group. The clobetasol propionatenaïve group tended to have less improvement than the previous use group; the previously exposed laser group had the most improvement (Table 4). A twoway analysis of variance for mean Skindex-29 overall score improvement showed no effect of prior clobetasol exposure, whereas treatment group had a significant effect without interaction effect. The change in outcomes between baselines and 6 months were similar between the clobetasol-naïve and -exposed groups (Table 5).

The Skindex-29 has clinically validated cutoff ranges for HRQOL categories, labeled as very little, mildly, moderately, and severely impaired beyond,

	Fractionated CO ₂	Clobetasol Steroid		
Outcome	Laser (n=27)	Cream (n=24)	Effect Size	Р
Skindex-29 score	40.51 ± 22.32	45.80±19.08	-5.29 (-16.94 to 6.37)	.371
Mean difference				
Skindex-29 score				
Emotion	42.69 ± 24.45	48.23 ± 22.58	-5.54 (-18.78 to 7.70)	.406
Symptoms	54.63 ± 20.98	55.95 ± 16.47	-1.32 (-11.89 to 9.24)	.805
Function	27.08 ± 25.72	34.03 ± 22.07	-6.95 (-20.39 to 6.51)	.309
Subjective VAS				
Ítching	7.07±3.12	7.25 ± 3.05	-0.18 (-1.92 to 1.57)	.840
Burning	5.93 ± 3.32	5.54 ± 3.24	0.39 (-1.46 to 2.23)	.678
Irritation or tearing	7.44 ± 2.53	7.42 ± 2.83	0.02 (-1.49 to 1.55)	.971
Pain with sex	4.71 ± 4.48	7.61±3.311	-2.9(-5.43 to -0.36)	.030
Tearing of vulvar skin	4.50±4.19	6.55 ± 2.60	-2.05 (-4.04 to -0.05)	.045
Dysuria	4.04 ± 3.62	4.04 ± 3.29	0 (-1.95 to 1.94)	.996
Painful	2.81 ± 3.37	3.00 ± 3.23	-0.19 (-2.07 to 1.70)	.845
defecation				
VSQ	9.54 ± 5.20	10.21 ± 5.59	-0.67 (-3.75 to 2.41)	.663
VHI	14.19 ± 4.95	14.75 ± 4.51	-0.56 (-3.23 to 2.10)	.674
Objective VAS				
White plaque	7.41 ± 2.04	6.25 ± 1.59	1.16 (0.13-2.18)	.030
Cigarette paper	7.11 ± 2.55	6.39 ± 1.85	0.72 (-0.54 to 1.98)	.266
Introital narrowing	4.78±2.72	4.50 ± 2.98	0.28 (-1.34 to 1.89)	.729
Perianal involvement	5.04 ± 3.49	4.75 ± 3.66	0.29 (-1.73 to 2.31)	.776
Loss of labial minora	6.63 ± 3.69	6.29 ± 3.17	0.34 (-1.59 to 2.27)	.729
Fusion of labia minora	3.48 ± 2.87	2.62 ± 2.68	0.86 (-0.71 to 2.42)	.279
Phimosis	6.27±3.84	5.88 ± 3.67	0.39 (-1.74 to 2.53)	.713
Fissure	4.78±2.85	4.00 ± 2.52	0.78 (-0.73 to 2.29)	.309
Erosion	2.55 ± 3.21	1.08 ± 2.39	1.51 (-0.08 to 3.09)	.066

Table 2. Comparison of Outcome Measures by Treatment Group and Stratification at Baseline

VAS, visual analog scale; VSQ, Vulvovaginal Symptom Questionnaire; VHI, Vaginal Health Index.

Data are mean±SD or difference (95% CI) unless otherwise specified.

* Participants who were previously exposed to clobetasol propionate.

⁺ Participants who have never used clobetasol propionate.

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calculated statistical significance using anchor-based interpretation. This study was powered for the detection of a mean difference of 16 points on Skindex-29 to correlate with decreasing two HRQOL categories.^{21,22} Skindex-29 scores for overall, emotion, and symptoms decreased by more than 16 points in the laser arm, whereas maximum improvement in the steroid arm was only 6.7 points (Table 3). However, the size effect between treatment groups was less than 16 points for primary outcome, overall Skindex-29 score. All four laser arm Skindex-29 scores had a decrease of at least one HRQOL category and the 6-month scores were in the least significant bother "very little" category. The steroid arm only showed improvement in HRQOL categories for overall and functional scores, Figure 2.

The VSQ secondary patient symptom outcome mean score changed from baseline to 6 months, with a significant difference in laser (-3.93 ± 4.12)

compared with steroid $(-0.58\pm5.11; P=.014)$, with more negative scores indicating greater improvement. Significant differences were also found in patient subjective VAS mean difference for irritation or tearing (Table 3). Dyspareunia data were not analyzed because 11 patients omitted the question, indicating abstinence.

Secondary outcomes for physician assessment scores found a significant difference in mean change of VHI score between baseline and 6 months in laser (1.92 ± 4.34) compared with steroid $(-0.43\pm3.62;$ P=.046), with a lower score corresponding to greater urogenital atrophy. Clinical interpretation of the VSQ and VHI have not yet been established. A significant difference was noted in physician VAS for erosion and phimosis; however, groups had similar scores with respect to white plaque, cigarette paper, introital narrowing, perianal involvement, loss and fusion of labia minora, and fissures. Worsening from baseline

	Exposed*	Naïve [†]	54 4 61	0
Outcome	(n=2/)	(n=24)	Effect Size	P
Skindex-29 score	29.70±21.11	33.11±24.92	-3.41 (-16.52 to 9.70)	.599
Mean difference				
Skindex-29 score				
Emotion	27.41±22.28	36.56±26.18	-9.15 (-22.95 to 4.64)	.183
Symptoms	42.20±22.76	41.37±23.02	0.83 (-12.09 to 13.74)	.898
Function	21.84±23.84	22.66±26.17	-0.82 (-14.99 to 13.35)	.907
Subjective VAS				
Ítching	4.59 ± 3.41	4.78±3.40	-0.19 (-2.13 to 1.75)	.845
Burning	3.74±3.61	4.04±3.23	-0.3 (-2.25 to 1.64)	.758
Irritation or tearing	4.48 ± 3.45	4.77 ± 3.60	-0.29 (-2.33 to 1.75)	.774
Pain with sex	5.18 ± 4.85	5.73 ± 3.90	-0.55 (-3.72 to 2.61)	.725
Tearing of vulvar skin	3.77±4.18	4.19±3.78	-0.42 (-2.76 to 1.92)	.722
Dysuria	2.07±3.21	3.22 ± 3.15	-1.15 (-2.96 to 0.67)	.211
Painful	1.22 ± 2.26	2.75 ± 3.24	-1.53 (-3.25 to -0.19)	.063
defecation				
VSQ	7.19 ± 4.65	7.62 ± 5.42	-0.43 (-3.30 to 2.42)	.756
VHI	14.23 ± 5.50	16.43 ± 4.92	-2.20 (-5.2 to 0.79)	.148
Objective VAS				
White plaque	5.81 ± 2.33	4.83 ± 2.12	0.98 (-0.30 to 2.26)	.132
Cigarette paper	5.27 ± 2.25	4.22±2.09	1.05 (-0.20 to 2.30)	.098
Introital narrowing	3.73 ± 3.18	3.00 ± 2.34	0.73 (-0.86 to 2.32)	.370
Perianal involvement	3.73 ± 3.69	4.00±3.61	-0.27 (-2.4 to 1.86)	.801
Loss of labial minora	6.73 ± 3.27	4.39 ± 3.65	2.34 (0.3-4.34)	.022
Fusion of labia minora	3.85 ± 3.23	2.00 ± 2.73	1.85 (0.13-3.56)	.037
Phimosis	6.92 ± 2.73	4.13±3.78	2.79 (0.87-4.72)	.004
Fissure	2.46 ± 2.28	2.48±1.86	-0.02 (-1.21 to 1.17)	.978
Erosion	0.54 ± 1.48	0.52 ± 1.75	0.02 (-0.9 to 0.96)	.971

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	Fractionated CO ₂	Clobetasol Steroid		
Outcome	Laser (n=27)	Cream (n=24)	Treatment Effect	Р
Skindex-29 score	-16.83 ± 18.09	-5.92 ± 5.81	10.91 (3.42 to 18.41)	.007*
Mean difference				
Skindex-29 score				
Emotion	-19.63 ± 21.92	-6.77 ± 9.9	12.86 (3.38 to 22.34)	.011*
Symptoms	-21.03 ± 22.18	-4.91 ± 11.19	16.12 (6.33 to 25.91)	.002*
Function	-10.65 ± 18.97	-5.30 ± 8.64	5.35 (-2.86 to 13.57)	.210
Subjective VAS				
Ítching	-3.26 ± 3.75	-1.83 ± 2.75	1.43 (-0.42 to 3.29)	.136
Burning	-2.78 ± 3.76	-1.00 ± 3.21	1.78 (-0.20 to 3.78)	.081
Irritation or tearing	-4.15 ± 4.04	-1.32 ± 2.84	2.79 (0.80 to 4.77)	.009*
Pain with sex	-0.69 ± 2.95	-0.14 ± 1.35	0.55 (-1.34 to 2.44)	.535
Tearing of vulvar skin	-1.77 ± 3.55	-1.32 ± 4.07	0.45 (-1.91 to 2.82)	.693
Dysuria	-2.11 ± 3.47	-0.78 ± 2.37	1.33 (-0.34 to 3.00)	.127
Painful defecation	-1.11 ± 2.83	-1.00 ± 2.67	0.11 (-1.54 to 1.77)	.894
VSQ	-3.92 ± 4.12	-0.58 ± 5.11	3.34 (0.68 to 6.00)	.014*
VHI	1.92 ± 4.34	-0.43 ± 3.62	-2.35 (-4.64 to -0.07)	.046*
Objective VAS				
White plaque	-1.81 ± 1.70	-1.30 ± 1.96	0.51 (-0.56 to 1.57)	.341
Cigarette paper	-2.58 ± 1.92	-1.50 ± 1.90	1.08 (-0.04 to 2.19)	.058
Introital narrowing	-1.73 ± 2.82	-0.70 ± 2.16	0.18 (-1.17 to 1.53)	.160
Perianal involvement	-0.73 ± 3.49	-1.77 ± 3.35	0.85 (-0.73 to 2.42)	.300
Loss of labial minora	-0.96 ± 2.44	-0.78 ± 2.26	1.50 (0.23 to 2.76)	.792
Fusion of labia minora	-0.50 ± 2.50	0.35 ± 2.92	0.34 (-1.08 to 1.73)	.279
Phimosis	-1.28 ± 2.30	0.22 ± 2.04	1.5 (0.23 to 2.76)	.022*
Fissure	-2.12 ± 2.40	-1.78 ± 2.41	0.34 (-1.06 to 1.73)	.634
Erosion	-2.08 ± 2.86	-0.57 ± 1.88	1.51 (0.13 to 2.89)	.036*
PGI-I (better or much better)	23 (88.5)	13 (61.9)	4.72 (1.15 to 24.55)	.073
PGI-S (satisfied or very satisfied)	21 (80.8)	9 (40.9)	6.07 (1.75 to 24.01)	.011*
Adverse events	1*	1 [‡]	0	1

Table 3. Comparison of Outcome Measures by Treatment Group Between Baseline and 6 Months, Intention-to-Treat Analysis

VAS, visual analog scale; VSQ, Vulvovaginal Symptom Questionnaire; VHI, Vaginal Health Index; PGI-I, Patient Global Impression of Improvement; PGI-S, Patient Global Impression of Satisfaction.

Data are mean \pm SD, difference (95% CI) for continuous data, odds ratio (95% CI) for categorical data, n (%), or n unless otherwise specified. Negative values indicate improvement for Skindex-29, VAS, and VHS scores, because higher scores represent more severe symptoms.

* Statistically significant at $P \le .05$.

[†] Adverse event was minor burning and blistering at laser site. [‡] Adverse event was activation of genital herpes 1 week after starting steroid.

(positive value) for fusion of labia minora and phimosis was noted for the steroid group (Table 3). Photodocumentation of pretreatment and posttreatment vulvar appearance was collected (Fig. 3).

At 6 months, 89% (23/27) of laser participants rated their symptoms as "better or much better" on the PGI-I compared with 62% (13/24) of steroid patients (P=.073). Overall, 58% of participants were "satisfied or very satisfied" on PGI-S; however, significantly more participants (81%, 21/27) in the laser treatment group were "satisfied or very satisfied" compared with the steroid treatment group (41%, 9/24); P=.011.

There were no serious adverse events or deaths during the study period. There was one reported minor adverse event in the laser treatment group where a patient called to report burning, irritation, and poor healing at the laser treatment site and was treated with topical clobetasol steroid. One patient in the steroid group had activation of genital herpes 1 week after starting treatment, and the steroid was held until episode resolved. Another patient in the steroid group deviated study protocol and started oral steroids. Four patients in the trial (three in the laser group and one in the steroid group) reported starting estrogen therapy between baseline and at the 6-month visit; all but one patient discontinued before the 6-month follow-up.

DISCUSSION

This is a novel randomized controlled study of the use of fractionated CO_2 laser for treatment of lichen

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Fig. 2. Change in mean Skindex-29 scores from baseline to 6 months for health-related quality of life (HRQOL) categories. *Colored portions* represent the clinically validated cutoff values for HRQOL categories: very little, mildly, moderately, and severely impaired. *Arrows* indicate change from baseline (*dot*) to 6-month outcome (*arrowhead*). *Black arrows* represent the fractionated CO₂ (laser) treatment group, and *white arrows* represent the clobetasol propionate (steroid) treatment group. The laser treatment group had greater change in both overall and all subscores.

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sclerosus. Patients had a greater improvement of symptoms and physician visual assessment at 6 months in the laser treatment arm when assessed with multiple validated questionnaires for vulvovaginal symptoms and health. Only the steroid treatment arm had mean scores with worsening of symptoms at 6 months. Patients in the laser treatment group overall reported greater symptom improvement and satisfaction with treatment and were highly compliant despite the requirement for multiple treatment visits. Fractionated CO_2 laser treatment should be considered a treatment option for patients with lichen sclerosus.

We stratified randomization with prior clobetasol propionate treatment to decrease potential bias with differences between a potential "clobetasol nonresponder" phenotype patient. Additionally, because most patients are started on a trial of clobetasol at diagnosis, the randomization equally distributed patients with a new diagnosis of lichen sclerosus. Baseline characteristics were similar between clobetasol-exposed and clobetasol-naïve patients, indicating comparable disease severity before treatment; and the majority of change outcomes at 6 months were similar, decreasing the risk of bias based on clobetasol-exposure status. Similarly, the exposed to steroid group had similar duration of diagnosis and length of clobetasol use between groups. Linear mixed model analysis based on prior clobetasol propionate use showed that the greater improvement in the laser group effect was maintained only on the participants with prior use, as opposed to naïve patients. This may suggest that the laser treatment works best as an adjuvant therapy to clobetasol, although more research is needed to answer the specific question of laser, alone, compared with laser for steroid drug-delivery. Bizjak Ogrinc et al show great efficacy of the laser treatment (neodymium:yttrium aluminum garnet) with adjuvant clobetasol compared with a clobetasolonly control group. Their reported VAS scores were very similar to our results in both groups at 6 months, although our data suggest slightly greater improvement in sub scores for the laser arm, this may be due to our much greater 6-month followup rate in steroid arm for comparison.¹⁸

Fractionated CO_2 laser treatment did not demonstrate significant safety concerns or adverse

Exposed		sed*		Naï	ve [†]		
Skindex-29 Score	Laser (n=15)	Steroid (n=12)	₽ [‡]	Laser (n=12)	Steroid (n=12)	P [‡]	Interaction Effect P
Overall	-21.96 ± 20.25	-6.10 ± 4.95	.004	-10.42 ± 13.07	-5.73 ± 6.78	.395	.144
Emotion	-27.33 ± 24.83	-8.33 ± 9.00	.005	-10.00 ± 13.01	-5.21 ± 10.90	.479	.131
Symptoms	-24.76 ± 22.04	-1.79 ± 7.84	.002	-16.36 ± 22.40	-8.05 ± 13.37	.258	.151
Function	-14.03 ± 22.12	-6.25 ± 9.53	.189	-6.42 ± 13.89	-4.34 ± 7.97	.736	.505

 Table 4. Stratification of Prior Clobetasol Propionate Exposure Compared With Naïve for Mean Change in Skindex-29 Score Between Baseline and 6 Months

Data are mean±SD unless otherwise specified.

* Participants who were previously exposed to clobetasol propionate.

⁺ Participants who have never used clobetasol propionate.

 \pm Statistically significant at $P \leq .05$.

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	Mean Dif	ference		P *
Outcome	Exposed (n=27)	Naïve (n=24)	Treatment Effect	
Skindex-29 score	14.91±17.20	8.07±10.46	6.84 (-1.10 to 14.78)	.097
Mean difference				
Skindex-29 score				
Emotion	18.89 ± 21.42	7.60±11.99	11.29 (1.61-20.96)	.027
Symptoms	14.55 ± 20.56	12.20 ± 18.54	2.35 (-8.66 to 13.35)	.672
Function	10.57±17.82	12.20 ± 18.54	5.19 (-3.10 to 13.48)	.225
Subjective VAS				
Itching	2.93 ± 3.67	2.22 ± 3.03	0.71 (-1.20 to 2.61)	.465
Burning	2.48 ± 3.83	1.35 ± 3.27	1.13 (-0.88 to 3.15)	.270
Irritation or tearing	3.22±4.21	2.50 ± 3.23	0.72 (-1.42 to 2.86)	.512
Pain with sex	0.79 ± 2.01	0 ± 2.48	0.79 (-1.02 to 2.59)	.373
Tearing of vulvar skin	1.56 ± 3.63	1.60 ± 3.97	-0.04 (-2.36 to 2.28)	.972
Dysuria	2.19 ± 3.35	0.70 ± 2.51	1.49 (-0.18 to 3.16)	.086
Painful defecation	1.15 ± 2.99	0.95 ± 2.44	0.2 (-1.41 to 1.82)	.805
VSQ	2.93 ± 4.67	1.61 ± 4.68	1.32 (-1.45 to 4.08)	.346
VHI	-1.42 ± 4.67	-0.13 ± 3.43	-1.29 (-3.63 to 1.05)	.281
Objective VAS				
White plague	1.46 ± 1.98	1.70 ± 1.66	-0.24 (-1.28 to 0.81)	.659
Cigarette paper	2.00 ± 2.35	2.18 ± 1.44	-0.18 (-1.30 to 0.93)	.753
Introital narrowing	2.04±2.13	0.35 ± 2.76	1.69 (0.26-3.12)	.019
Perianal involvement	1.35 ± 3.93	1.05 ± 2.82	0.30 (-1.67 to 2.27)	.766
Loss of labial minora	0.77±1.88	1.00 ± 2.82	-0.23 (-1.63 to 1.17)	.734
Fusion of labia minora	0.31 ± 3.03	-0.13 ± 2.34	0.44 (-1.11 to 1.99)	.578
Phimosis	0.80 ± 2.60	0.30 ± 1.92	0.5 (-0.83 to 1.82)	.459
Fissure	2.92 ± 2.02	0.87±2.39	2.05 (0.77-3.33)	.002
Erosion	2.42 ± 2.98	0.17±1.15	2.25 (0.97-3.53)	.001
PGI-I (better or much better)	19 (70.4)	17 (85)	2.39 (0.58-12.26)	.31
PGI-S (satisfied or very satisfied)	16 (59.3)	14 (66.7)	1.37 (0.42–4.66)	.765

Table 5.	Comparison of Outcome Measures by Naïve or Exposed to Clobetasol Propionate Between
	Baseline and 6 Months, Intention-To-Treat Analysis

VAS, visual analog scale; VSQ, Vulvovaginal Symptom Questionnaire; VHI, Vaginal Health Index; PGI-I, Patient Global Impression of Improvement; PGI-S, Patient Global Impression of Severity.

Data are mean±SD, difference (95% CI) for continuous data, odds ratio (95% CI) for categorical data, or n (%) unless otherwise specified. Negative values indicate improvement for Skindex-29, VAS, and VHS scores, because higher scores represent more severe symptoms. * Statistically significant at $\dot{P} \leq .05$.

events during the trial 6-month time period. Laser treatment was well-tolerated in an outpatient setting, with only one minor adverse event including irritation, blistering, and burning. The current clinical climate cautions the use of energy-based intervention for non–U.S. Food and Drug Administration-approved indications; however, lichen sclerosus is a defined gynecologic pathology. We hope to add quality research to the investigation of this new technology.²⁷ The effect of laser therapy on the risk of vulvar squamous cell carcinoma is unknown and further research required. Fractionated CO_2 technology is currently offered by a range of health care professionals including gynecologist, plastic surgeons, dermatology, and aestheticians. However, treatments are not covered by insurance, and out-of-pocket cost may limit this resource for patients. We hope that with good quality evidence for efficacy, insurance companies will consider coverage of this technology for lichen sclerosus, a diagnosis with no second-line treatment options.

This study is limited by short-term 6-month follow-up; therefore, the treatment effect duration is still unknown. The study was unblinded for patients and evaluators and was only performed at a single center. The steroid group had more noncompliant patients (25% vs 4%), and this could have contributed to large effect size between groups; however, nonadherence to topical steroid treatments is very common in clinical practice. The Skindex-29 is a quality-of-life measure, and we found significant improvement above that of the other subjective and objective measures with lesser effect size. It is possible, some of the subjective

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Fig. 3. Photo documentation of a patient at baseline (**A**) and 6 months (**B**) in the laser treatment group. Visual improvement in elasticity of vulvar skin, decreased fissuring, and increased vascularization were seen after laser treatment between baseline and 6 months.

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improvement was biased by ease or satisfaction with treatment and desire for the novel treatment approach. We limited our investigation to only postmenopausal women to not introduce other confounding variables present in a broader population. Further research using placebo and sham lasers for treatment blinding is needed. Patients previously using topical vaginal estrogen were continued on prior treatment. Groups were not stratified based on estrogen exposure; however, there was equal use reported between groups.

Strengths of the study include the use of organized validated subjective and objective assessment tools. In addition, this adds to the lichen sclerosus literature with robust randomized controlled trial methods directly comparing a new treatment to the gold-standard clobetasol treatment.

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Authors' Data Sharing Statement

- Will individual participant data be available (including data dictionaries)? *Yes.*
- What data in particular will be shared? *Deidentified baseline characteristics, symptom and objective scores at baseline and 6 months. Photo documentation will not be shared.*
- What other documents will be available? None.
- When will data be available (start and end dates)? November 2020–May 2022.
- By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? Scientific investigators must file for IRB approval and data sharing secondary analysis request through main institution IRB.

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