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ORIGINAL STUDY

Effect of rescue fractional microablative CO_2 laser on symptoms and sexual dysfunction in women affected by vulvar lichen sclerosus resistant to long-term use of topic corticosteroid: a prospective longitudinal study

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Abstract

Objective: The objective of this study was to evaluate the efficacy of rescue fractional microablative CO_2 laser treatment in women with severe symptoms and sexual dysfunction related to lichen sclerosus not responsive to long-term ultra-potent topical corticosteroid treatment.

Methods: Consecutive eligible women with lichen sclerosus referred to our unit who received fractional microablative CO_2 laser treatment after failure of ultra-potent topical corticosteroid treatment were enrolled in the study. The diagnosis was confirmed by histological assessment in all cases. Patients underwent two cycles of CO_2 laser every 30 to 40 days. The severity of lichen sclerosus-related symptoms, sexual function, and procedure discomfort were evaluated with a visual analog scale in the same individual at baseline, after completion of each treatment cycle. Follow-up visits were scheduled during each treatment cycle and at least 1 month after completion of the treatment. The Friedman ANOVA test was used to evaluate differences in the visual analog scale scores of each symptom during treatment.

Results: A total of 100 patients with vulvar lichen sclerosus were screened, 40 of whom fulfilled the eligibility criteria. We found a significant improvement in vulvar itching (χ^2 [2] = 31,182, $P < 0.001$), vulvar dryness (χ^2 [2] = 40,364, $P < 0.001$), superficial dyspareunia (χ^2 [2] = 37,488, $P < 0.001$), and sensitivity during intercourse (χ^2 [2] = 22,143, $P < 0.001$) after two CO_2 laser cycles. Pain related to probe movement and laser application was low and did not change significantly consequent to treatment. No systemic or local adverse effects occurred during or after laser treatment.

Conclusion: Fractional microablative CO_2 laser treatment is safe and might represent an effective rescue procedure for patients suffering from lichen sclerosus who fail to respond to long-term ultra-potent topical corticosteroid treatment. These preliminary findings require further study with adequately powered randomized controlled trials.

Key Words: CO_2 laser – Lichen – Lichen sclerosus – Topical steroids – Vulvar disorders.

Lichen sclerosus is a chronic disorder that mainly affects the vulva skin.[1] This condition usually occurs after the fifth decade of life but can occur before puberty.[2] The most common symptoms are burning, dyspareunia, and itching. The affected skin is usually white and thin like ''cigarette paper,'' or is characterized by porcelain-white papules and plaques.[1] This condition can lead to such alterations of genital structure as fusion of the vulva lips, clitoris burying, disruption of the vulvar opening, and a significant reduction of vulvar tropism.[3] These alterations can negatively affect quality of life and sexual function, thereby causing relational couple discomfort and impaired psychological well-being.[1,4,5] Furthermore, long-term vulvar lichen sclerosus has been associated with a low, albeit significant, risk of vulvar cancer.[6-9]

The cause of lichen sclerosus is unknown, and 21.5% to 34% of cases are associated with autoimmune diseases, namely thyroid disease, alopecia areata, vitiligo, and pernicious anemia.[10,11] The recommended treatment for lichen sclerosus is ultra-potent topical corticosteroids (UP-TCs) (clobetasol

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propionate and mometasone furoate) and pimecrolimus.[11,12] Concerns have, however, been raised regarding the long-term use of UP-TCs because they may induce vulvar atrophy, and thereby exacerbate lichen sclerosus symptoms.[1,13,14] Furthermore, these medications have been associated with contact sensitization, skin changes, and secondary infection.[1,15,16] Currently, clinicians have few rescue strategies for patients who do not respond adequately to UP-TCs after their long-term use.[1]

Fractional microablative CO_2 laser is an innovative approach to vaginal itching and has proven to be effective in iatrogenic and menopausal vulvovaginal atrophy.[17] It promotes the production of collagen and elastic fibers thereby restoring epithelial trophism.[18] Thus far, the few case reports that explored the efficacy of fractional microablative CO_2 laser in women affected by lichen sclerosus produced conflicting results.[18] The objective of our study was to evaluate the efficacy of rescue fractional microablative CO_2 laser in treating the symptoms and sexual dysfunction in women with lichen sclerosus nonresponsive to long-term use of UP-TCs.

MATERIALS AND METHODS

The study population was selected from among all consecutive women with vulvar lichen sclerosus referred to the Reproductive Medicine Unit of the University of Naples Federico II between December 1, 2017 and May 1, 2019 who received fractional microablative CO_2 laser treatment after failure of long-term treatment with clobetasol propionate (0.05% ointment applied locally every night for 4 weeks, and subsequently on alternate nights for 4 wk). Patients who did not report any symptom improvement and in whom no objective visual response was found during vulvar evaluation after at least four treatment cycles were deemed corticosteroid refractory. Before recruitment, all women underwent a basal gynecological examination, and all had a negative Pap test result in the last 3 years. We included only women older than 35 years in whom the diagnosis of lichen sclerosus was confirmed by histological assessment. Given the association between the estrogen transduction pathway and the development of lichen sclerosus,[19,20] we decided to exclude women who had undergone any kind of postmenopausal hormone therapy or contraception treatment for at least 1 year before the procedure to avoid confounding factors. We also excluded women with concomitant malignant and nonmalignant lower genital tract lesions. Lastly, we did not include patients with congenital/acquired immunodeficiency.

The women enrolled in this study underwent two cycles of fractional CO_2 laser treatment at an interval of 30 or 40 days. In detail, vulvar lesions were treated without sedation and local anesthesia, at the following settings: power 25 V, scan time 1000 μs, dot spacing 700 μm, and the smart stack parameter from 1 to 3. In menopausal women, menopause-related vaginal manifestations were also treated using a dot power 30 V, scan time 1000 μs, dot spacing 1000 μm, and the smart stack parameter from 1 to 3, as previously reported.[17]

Follow-up assessments of symptoms were scheduled. This consisted in gynecologic assessment planned before and 3 months after each treatment cycle (median follow-up of 5 mo). All procedures were performed by the same operator (T.P.). We evaluated the most common symptoms of lichen sclerosus and tolerability of laser treatment using a visual analog scale (VAS) as described previously[17,21] at each treatment cycle. The VAS score was measured by a trained interviewer (F.S.). The primary outcome was vulvar itching. Secondary outcomes were superficial dyspareunia (pain at the introitus during intercourse), vulvar dryness, vulvodynia, reduced sensitivity during intercourse, and tolerability of laser treatment (pain during probe application and/or movement and laser-associated pain). Symptoms related to menopause, namely dysuria, vaginal laxity, and vaginal discharge were also analyzed.

Given the observational nature of the study, under Italian law, it is not subject to ethics approval. All participants gave their written informed consent to the study. This study conforms to the principles embodied in the Declaration of Helsinki.

Statistical analysis

In this study we compared paired data from the same individual at different time points, so that each patient served as a ''self-control.'' In detail, the median and interquartile range VAS score for each lichen-related, procedure-related symptom and menopausal symptoms were calculated during the first visit and after completion of each of the two treatment cycles. The Friedman ANOVA test was used to evaluate differences in the median VAS scores of each symptom during treatment. Pairwise comparison between treatment cycles was also performed. Results were analyzed using the statistical package SPSS 22 for Windows (Statistical Package for the Social Sciences, IBM, New York). A P value <0.05 was considered statistically significant.

RESULTS

A total of 100 patients with vulvar lichen sclerosus were screened. Forty of them fulfilled the eligibility criteria (Fig. 1). Most were in menopause (37/40). All women provided informed consent to laser procedures. None of the women enrolled in the study reported any allergic manifestation to corticosteroids during previous treatment. The mean age of the population was 57.9 ± 11.1 years. As reported in Table 1, at baseline, women enrolled in the study had severe lichen-related symptoms, namely, vulvar itching (median VAS score 8, interquartile range 7-9), vulvar dryness (median VAS score 8, interquartile range 8-9), superficial dyspareunia (median VAS score 9, interquartile range 7-10), and reduced sensitivity during intercourse (median VAS score 6, interquartile range 3-9). After completion of treatment, there was a significant improvement in vulvar itching (χ^2 [2] = 31,182, $P < 0.001$), vulvar dryness (χ^2 [2] = 40,364, $P < 0.001$), superficial dyspareunia (χ^2 [2] = 37,488, $P < 0.001$), and better sensitivity during intercourse (χ^2 [2] = 22,143, $P < 0.001$) (Table 1 and Fig. 2). Follow-up analysis with pairwise comparison of vulvar itching showed an improvement in terms of vulvar itching after the first treatment cycle

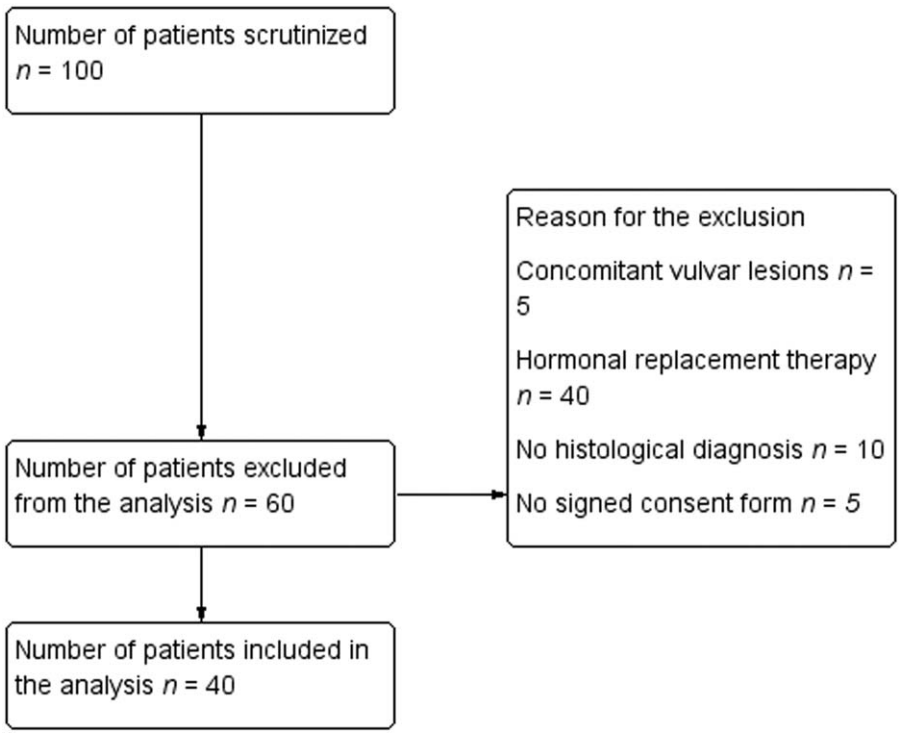

FIG. 1. Flow chart illustrating enrollment criteria.

(median value T0 = 8 vs median value T1 = 6, $P = 0.037$). An additional improvement was recorded after completion of the second cycle (median value T0 = 8 vs median value T2 = 3, $P < 0.001$). Similarly, vulvar dryness, sensitivity during intercourse, and superficial dyspareunia improved progressively after two treatment cycles (Fig. 2). No appreciable benefit was observed in terms of vulvodynia ($P = 0.22$). Pain related to probe movement and laser application was low and did not significantly change consequent to treatment (Table 2). No patient reported any systemic or local adverse effect during or after completion of laser treatment.

DISCUSSION

This study shows that fractional microablative CO_2 laser treatment might relieve most of the symptoms related to lichen sclerosus in women refractory to UP-TCs, which are

TABLE 1. *Median visual analog scale scores of lichen sclerosus-related symptoms at baseline (T0) and after two cycles of laser treatment (T1 and T2)*

	T0 (n = 40) (VAS range 0-10)		T1 (n = 40) (VAS range 0-10)		T2 (n = 40) (VAS range 0-10)					
Lichen sclerosus-related symptoms	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	T0 vs T1 vs T2 P^a	T0 vs T1 P^a	T0 vs T2 P^a	T1 vs T2 P^a
Vulvar itching	8	7-9	6	5-6	3	1-4	<0.001	0.037	<0.001	0.01
Vulvar dryness	8	8-9	7	5-7	3	1-5	<0.001	NS	<0.001	0.01
Superficial dyspareunia	9	7-10	7	5-8	3	2-6	<0.001	0.037	<0.001	0.002
Reduced sensitivity during intercourse	6	3-9	4	1.75-7	2	0-3.25	<0.001	NS	<0.001	0.025
Vulvodynia	0	0-7	1	0-5	1	0-3	0.22	NS	NS	NS
	T0 (n = 37) (VAS range 0-10)		T1 (n = 37) (VAS range 0-10)		T2 (n = 37) (VAS range 0-10)					
Menopause-related symptoms	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	T0 vs T1 vs T2 P^a	T0 vs T1 P^a	T0 vs T2 P^a	T1 vs T2 P^a
Vaginal laxity	0	0-1	0	0-3	0	0-2	0.038	NS	0.02	0.04
Dysuria	1	0-5	0	0-7	0	0-3	0.01	NS	0.04	0.05
Vaginal discharge	1	0-3	1	0-3	0	0-3	0.034	NS	0.04	NS

NS, not significant; VAS, visual analog scale.
[a]Friedman ANOVA test.

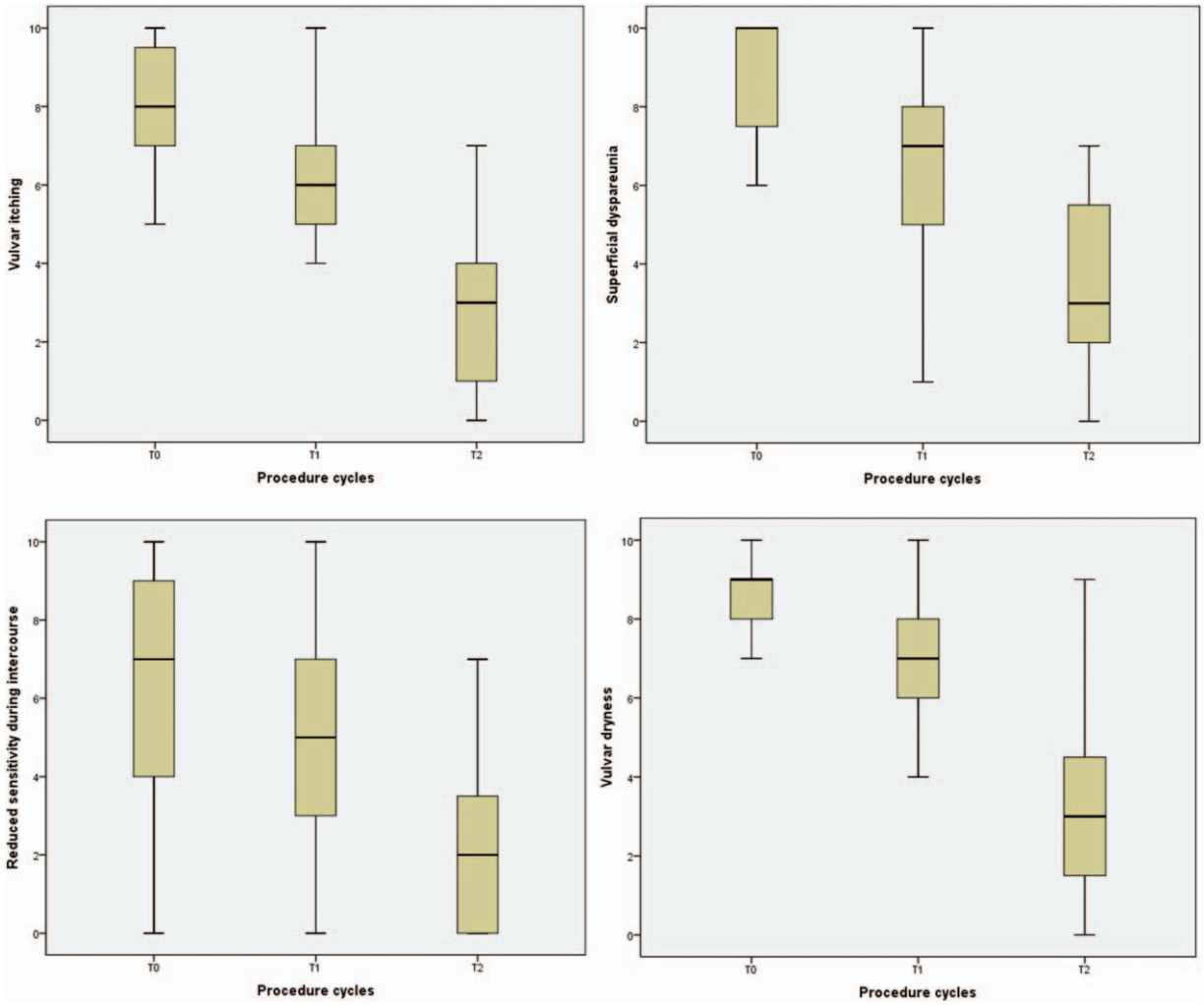

FIG. 2. Box whisker plot of the visual analog scores of vulvar itching, superficial dyspareunia, lack of sensitivity during intercourse and vulvar dryness at baseline (T0) and after the first (T1) and second cycles (T2).

considered the first-line approach to this condition.[22] Symptom relief was significant after two treatment cycles. No adverse effects occurred, and the procedure was well tolerated. Notably, no analgesia or any form of sedation was required during the procedure.

CO_2 surgery was first used more than 20 years ago to treat a severe case of penile lichen sclerosus (balanitis xerotica obliterans) with minimal operative discomfort and excellent cosmetic results, which were subsequently confirmed.[23,24] On the contrary, the results of CO_2 surgery in women are somewhat inconsistent. Kartamaa and Reitamo[23] reported recurrence in two of five treated patients. More recently, Lee et al[18] reported positive results in five women, four of whom were treated with fractional microablative CO_2 laser. The latter results have recently been questioned because the patients' symptoms were not measured objectively, and

TABLE 2. *Median visual analog scale scores of procedure-related symptoms at after the first (T1) and the second CO_2 cycles (T2)*

	T1 (n = 40) (VAS range 0-10)		T2 (n = 40) (VAS range 0-10)		
Procedure-related symptoms	Median	Interquartile range	Median	Interquartile range	P^a
Pain during probe application	1	0-2	0	0-1	0.058
Pain during probe movements	0	0-1	0	0-0	NS
Laser-associated pain	0	0-1.75	0	0-1	NS

NS, not significant; VAS, visual analog scale.
[a]Friedman ANOVA test.

because the patients received concomitant treatment with steroids.[25]

The mechanism of action of CO_2 laser treatment in lichen lesions is not clear. This procedure induces the absorption of light energy by water molecules in the epidermis, thereby leading to the ablation of the epidermis and superficial dermis.[26] Consequently, it is feasible that CO_2 laser treatment may reduce the hyperkeratosis of lichen lesions and so improve repair and re-epithelialization processes.[18]

Our results indicate that fractional microablative CO_2 laser treatment could significantly improve lichen-related symptoms and could therefore be considered a rescue strategy for pain relief and sexual discomfort in patients. To our knowledge, this is the largest study conducted so far to evaluate the efficacy of rescue fractional microablative CO_2 in a selected cohort of women affected by lichen sclerosus and could represent a preliminary step to more robust trials. In addition, considering that steroid therapy is not free of side effects,[1] and the interesting safety profile of laser surgery, randomized or large prospective trials comparing the two strategies might yield information also in naïve women without neoplastic lesions. Nonetheless, we recognize that this study is limited by the nonrandomized design, the small sample size and the lack of an untreated control, or alternatively, the use of sham laser controls. Another limitation of our study is the short follow-up, namely a median of 5 months; consequently, we do not know the long-term effect of fractional microablative CO_2 laser, or whether additional treatment cycles would have a long-lasting effect.

CONCLUSIONS

In conclusion, our study suggests that fractional microablative CO_2 laser treatment could be a valid rescue strategy in patients affected by lichen sclerosus who do not respond to UP-TCs after long-term use. Our promising findings could encourage further investigations regarding this issue and could pave the way to an alternative strategy for the management of lichen sclerosus.

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