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RANDOMISED CONTROLLED TRIAL

Nd:YAG/Er:YAG dual laser compared with topical steroid to treat vulvar lichen sclerosus: A randomised controlled trial

Irena Zivanovic[1] | **Marianne Gamper**[1] | **Debra Fesslmeier**[1] | **Claudia Walser**[1] | **Sigrid Regauer**[2] | **Volker Viereck**[1]

[1]Department of Gynaecology and Obstetrics, Cantonal Hospital Frauenfeld, Frauenfeld, Switzerland

[2]Diagnostic and Research Institute of Pathology, Medical University Graz, Graz, Austria

Correspondence
Volker Viereck, Department of Gynaecology and Obstetrics, Cantonal Hospital Frauenfeld, Postfach, 8501 Frauenfeld, Switzerland.
Email: volker.viereck@stgag.ch

Abstract

Objective: To evaluate the efficacy and safety of a novel non-ablative Nd:YAG/Er:YAG dual laser treatment for vulvar lichen sclerosus (LS) in comparison with the recommended first-line therapy with topical steroid.

Design: A randomised investigator-initiated active-controlled trial.

Setting: Single tertiary referral centre.

Population: Women with vulvar LS.

Methods: Randomisation (2:1) to Nd:YAG/Er:YAG laser therapy or topical clobetasol proprionate therapy. Four laser treatments at 0, 1, 2 and 4 months or decreasing doses of steroid for 6 months.

Main Outcome Measures: The primary outcome was the change in objective validated clinical LS score in the laser arm between baseline and 6 months. Secondary outcomes were laser tolerability/safety, symptom scores and patient satisfaction.

Results: Sixty-six women were included, 44 in the laser group and 22 in the steroid group. The total LS score decreased by −2.34 ± 1.20 (95% CI −2.71 to −1.98) in women treated with laser compared with a decrease of −0.95 ± 0.90 (95% CI −1.35 to −0.56) in those receiving steroid applications ($p < 0.001$). Laser treatment was safe and well tolerated. Subjective severity scores (on visual analogue scale) and vulvovaginal symptoms questionnaire scores improved similarly for the laser and steroid arms without significant differences between the two treatments. Patient satisfaction was higher in the laser arm than in the steroid arm ($p = 0.035$).

Conclusions: Non-ablative dual Nd:YAG/Er:YAG laser therapy was safe and significantly improved clinical outcome and subjective symptoms at the 6-month follow up. This suggests that laser may be a promising alternative to corticosteroid therapy. However, the authors caution regular follow ups because of the premalignant nature of the disease.

KEYWORDS

clobetasol propionate, laser safety, lichen sclerosus, non-ablative Nd:YAG/Er:YAG laser therapy, prospective randomised controlled trial, steroid therapy

Trial Registration: ClinicalTrials.gov NCT03926299.

1 | INTRODUCTION

Lichen sclerosus (LS) is an inflammatory scarring dermatosis, characterised by a lymphocytic response that has a predilection for the genital skin.[1] Even though early LS has a potential for remission, it can, if untreated, progress to irreversible structural changes, including resorption of labia minora, agglutination of the clitoral hood, and stenosis of introitus and urethra.[2] If untreated, patients with LS have a 3.5%–5% lifetime risk of developing squamous cell carcinoma.[1,3]

The recommended first-line therapy for LS is the topical application of potent corticosteroids.[2,4] Corticosteroid therapy reduces inflammation, alleviates symptoms, prevents disease progression and reduces malignant potential, but needs to be continued for life.[3] Some patients may have a negative attitude towards corticosteroid therapy that can result in noncompliance and steroid phobia, and in some cases, steroids may not help.[5–7] Laser therapy may offer a novel alternative treatment option for vulvar LS.[6] Most cohort studies and randomised controlled trials (RCTs) used the fractionated ablative CO_2 laser (10 600 nm).[8–13]

In this study, we investigated the safety, tolerability and efficacy of a novel dual neodymium:yttrium–aluminium–garnet (Nd:YAG)/erbium:yttrium–aluminium–garnet (Er:YAG) laser concept for the treatment of vulvar LS. In contrast to the CO_2 laser, the non-ablative Nd:YAG laser beam (1064 nm) penetrates through hyperkeratotic and sclerotic tissue layers without damaging the sensitive vulvar epithelium. The Nd:YAG laser is emitted with a long pulse duration in order to induce a homogeneous heat response in the deep subepithelial regenerative dermis (>5 mm). This leads to collagen remodelling and neovascularisation.[5,14,15] Epithelial hyperkeratosis, epithelial hyperplasia and other skin irregularities are removed by the additional ablative Er:YAG laser step (2940 nm).[15]

The study was designed as an RCT to compare the Nd:YAG/Er:YAG laser with the recommended first-line therapy for vulvar LS. We hypothesise that the dual laser therapy is effective and safe, and produces similar results to the steroid treatment.

2 | METHODS

2.1 | Study design and participants

This study is an investigator-initiated, single-centre, active-controlled RCT carried out at an ambulatory tertiary referral centre. The study received institutional ethics approval (EKOS 19/056, BASEC-ID: 2019-00634) and was registered at ClinicalTrials.gov (www.clinicaltrials.gov, NCT03926299). Patients gave informed consent. The clinical study protocol was published.[16,17] The recommendations of the Consolidation Standards of Reporting Trials (CONSORT) statement were followed for the reporting of this trial (Figure 1).[18] The study protocol and statistical analysis plan are available as Appendix S1.

Women with a clinical diagnosis of vulvar LS and a physician-administered clinical LS score ≥4[19,20] were eligible. The total LS score includes the evaluation of six clinical parameters: (1) erosions, (2) hyperkeratosis, (3) fissures, (4) agglutination, (5) stenosis and (6) atrophy (vulvar architectural changes such as shrinkage of labia minora and clitoris, but also pale, dry and thin vulvar skin with reduced elasticity[21]). Each parameter is scored as 0 (normal/none), 1 (a few signs/moderate), or 2 (clear signs/severe).[4,19,20,22,23] The total LS score therefore has a range of 0 (normal) to 12 (most severe). A total LS score of ≥4 identifies LS with a probability of >90%.[19] Although this LS score is not a universally accepted tool, it was validated for clinical diagnosis and evaluation of LS[22] and has been used in several clinical LS studies.[4,10,13,23] A biopsy is indicated if there is doubt about the clinical diagnosis, in the case of no treatment response or if (pre-)malignancy is suspected.[2,22]

To avoid treatment interference, previous steroid application was stopped ≥6 weeks before baseline.[2,9,10,16] Exclusion criteria were any concomitant topical or systemic treatment for LS, acute or recurrent urogenital infections, a body mass index >35 kg/m^2, ≤3 months since childbirth/miscarriage/operation in the lower abdomen, pregnancy, breastfeeding or the intention to become pregnant during the study, start of vaginal estrogen treatment in the preceding 3 months, presence of contraindications for the laser treatment, precursor/malignant disease as the cause of the symptoms and any condition interfering with study compliance.

2.2 | Patient involvement

At the screening visit 1 month before the baseline visit (Figure 2), patients gave informed consent for participating in the trial and for publication of the pseudonymised data. After publication, participants will receive details of the results in an article/newsletter, a webinar broadcast, an internet post or a talk suitable for a non-specialist audience.

2.3 | Randomisation

At the baseline visit, eligible participants were randomised to the laser or the steroid arm in a proportion of 2:1. Patients were stratified by the severity of their clinical LS score (4–6: LS low score [LSL]; ≥7: LS high score [LSH]). To reach an LS score of ≥7 (LSH) at least one of the six LS score criteria had to be rated as 2 (severe). Block randomisation was applied for each stratum. The study coordinator without patient contact organised the randomisation process. Consecutively labelled and sealed envelopes for each stratum were opened in subsequent order by the study doctor. Because of the completely different treatment arms, patients were not blinded. Two study doctors independently scored the clinical findings.

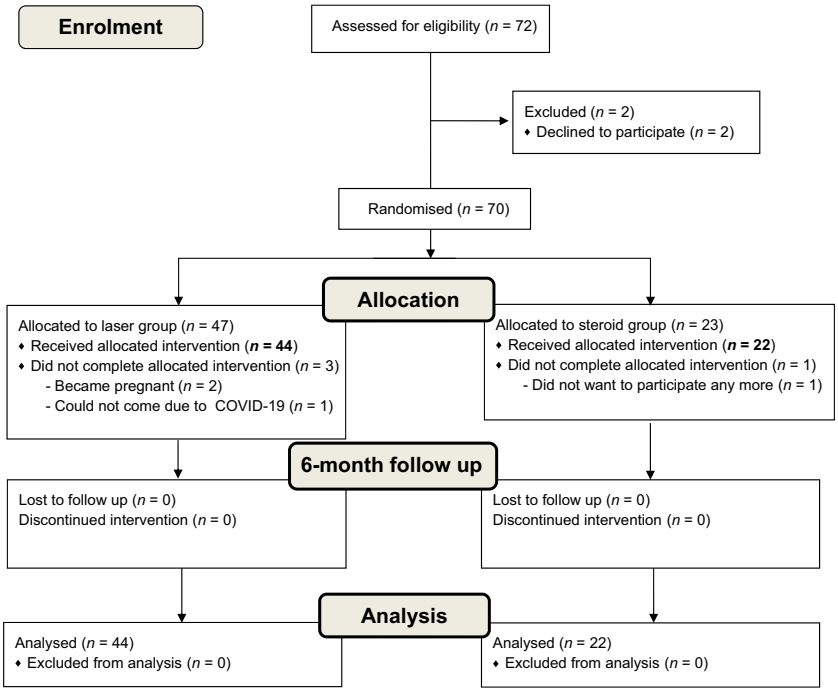

FIGURE 1 CONSORT (Consolidated Standards of Reporting Trials) flow diagram.[18]

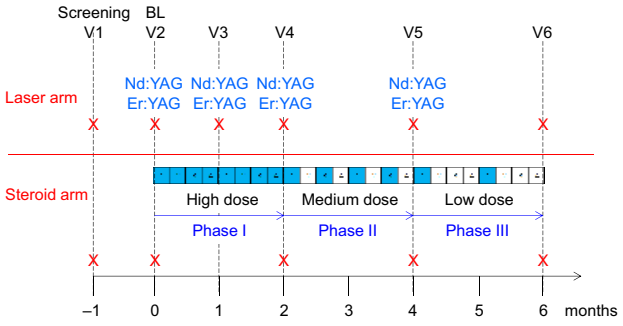

FIGURE 2 Study design. Patients with LS were randomised to the laser or steroid arm. They received either Nd:YAG/Er:YAG laser treatment at baseline, and at months 1, 2 and 4, or de-escalation doses of high-potency topical steroid (phase I: 4 days/week for 8 weeks; phase II: 4 days/week every 2nd week for 8 weeks; phase III: 4 days/week every 4th week for 8 weeks). Follow-up assessment was at month 6. BL, baseline; X, study visits V1–V6. Patients in the steroid arm had no V3.

2.4 | Study plan and intervention

Patients in the laser group received four laser treatments with the dual Nd:YAG/Er:YAG laser (FotonaSmooth SP® Spectro laser, Model M021-4AF/3), at baseline and after 1, 2 and 4 months. This laser device is investigational for the treatment of vulvar LS. The comparison group received standardised topical steroid for 6 months. Outcome was analysed at the follow-up visit at month 6 (Figure 2).[16,17]

The non-ablative Nd:YAG laser treatment was applied as five brushings with the non-contact R33 handpiece/9-mm spot size. The laser was set to PIANO mode (long 5-s pulses) and a fluence between 70 and 100 J/cm^2, starting with a low fluence in the first laser session, but increasing in later sessions depending on the patient's tolerance. The subsequent ablative Er:YAG laser treatment removed superficial irregularities with the R11 handpiece/5-mm spot size. The laser was set to MSP mode (short 100-µs pulses), 2 Hz and a fluence between 1 and 3 J/cm^2, depending on the patient's tolerance.[16] Tolerability was assessed by registration of discomfort/pain (visual analogue scale [VAS] 0–10) and adverse events during and immediately after each laser session and by recording the (optional) use of local anaesthetics before/during the laser session.

Patients in the steroid arm were treated according to the Swiss standard interval scheme of the University Hospital Zürich. Topical clobetasol 0.05% ointment or cream was applied on four evenings per week, every week for months 1 and 2 (phase I), on four evenings per week every other week for months 3 and 4 (phase II), and on four evenings per week in the first week of the month for months 5 and 6 (phase III) (Figure 2).[16,17,24] Patients were allowed to use additional clobetasol if symptoms persisted after 14 days, either on the three clobetasol-free (interval) days, or in the interval weeks or up to twice daily. They were instructed to accurately document all treatments in a chart.

2.5 | Outcomes and outcome measures

The primary outcome was the change of the objective clinical LS score in the laser arm between baseline and 6 months. Secondary outcomes were changes in subjective and objective measures between baseline and 6-month follow up, safety of the laser treatment and comparisons between laser

TABLE 1 Baseline demographics.

Variable	Total ($n=66$)	Laser ($n=44$)	Steroid ($n=22$)	p (t test)
Age mean ± SD (years)	59.3 ± 15.9	57.9 ± 16.4	62.2 ± 14.4	0.303
Postmenopausal, n (%)	47 (71%)	31 (70%)	16 (73%)	0.850
BMI mean ± SD (kg/m^2)	25.6 ± 4.6	25.4 ± 4.5	26 ± 4.9	0.612
Median parity (IQR)	2 (1–2)	2 (1–2)	2 (1–2.8)	0.560
Median duration of symptoms (IQR) (years)	5 (2–9)	4 (2–7)	6 (3–10)	0.171
Median duration since LS diagnosis (IQR) (years)	2 (1–5)	2 (1–4)	3 (0.3–8)	0.075
Family history of LS, n (%)	9 (14%)	5 (11%)	4 (18%)	0.454
Local estrogen use, n (%)	38 (58%)	24 (55%)	14 (64%)	0.489
Smoker former and current, n (%)	19 (29%)	11 (25%)	8 (36%)	0.344
Diabetes, n (%)	2 (3%)	2 (5%)	0 (0%)	0.317
Recurrent UTI, n (%)	5 (8%)	5 (11%)	0 (0%)	0.103
LSH[a], n (%)	26 (39%)	17 (39%)	9 (41%)	0.861
With intercourse, n (%)	36 (55%)	27 (61%)	9 (41%)	0.119

Abbreviations: BMI, body mass index; IQR, interquartile range; LS, lichen sclerosus; LSH, clinical LS score high; SD, standard deviation; UTI, urinary tract infection.
[a]LSH (clinical LS score ≥7); LSL (clinical LS score 4–6).

and steroid outcomes.[16] No core outcome set was used as no such set was available for this condition.

Subjective symptoms were graded on a VAS. The VAS score included three items (vulvar itching, burning, pain) and a fourth item (dyspareunia) for those who were sexually active and engaging in vaginal intercourse. Each symptom was scored from 0 (none) to 10 (extreme), thus yielding a range of 0 (no symptoms) to 30 (most extreme) for assessing itching, burning and pain. VAS pain at intercourse was scored separately from 0 (no pain) to 10 (most extreme pain) for sexually active individuals.

Additionally, subjective outcome was evaluated with the vulvovaginal symptoms questionnaire (VSQ), which is a 21-item questionnaire representing vulvovaginal symptoms (questions 1–7), emotions (questions 8–11), life impact (questions 12–16) and sexual impact (questions 18–21).[16,25,26] VSQ questions 1–16 were evaluated for all patients, with a score range from 0 (normal) to 16 (most severe). VSQ questions 18–21 were evaluated for those with intercourse, with a score range from 0 (normal) to 4 (most severe).

Patient satisfaction was evaluated by the Patient Global Impression of Improvement questionnaire (PGI-I).[27] Patients rated their situation at 6 months in comparison to before the laser or steroid intervention on a 7-point Likert scale as 'very much better', 'much better', 'a little better', 'no change', 'a little worse', 'much worse' or 'very much worse'.

2.6 | Statistical analysis

Sample size calculation was performed for the primary end point, which was the change of severity of the total LS score after 6 months. A total of 34 patients in the laser arm would provide 80% power to detect a medium effect size of 0.5[28] with a two-sided α set at 5%. Assuming a drop-out rate of 10%–15%, 40 patients were needed in the laser arm.

Demographics were calculated as mean ± standard deviation (SD), median (interquartile range [IQR]) or number (%) of all patients at baseline and according to treatment group. Means ± SD of all outcomes were compared between groups at baseline and at 6 months as well as within groups between baseline and 6 months. Wilcoxon signed-rank test (paired) was used to compare time-points within groups and Wilcoxon rank sum test (non-paired) was used to compare groups at each time-point. Mean differences (change) between baseline and 6 months were compared for all outcomes between groups.

The percentage of patients with VAS or VSQ improvements ≥50% at 6 months compared with baseline were calculated for both treatment groups. A 50% reduction in severity for VAS or VSQ was regarded as clinically effective.[29] R version 4.1.1. was used for Wilcoxon tests, effect size calculation and ordinal regression analysis, while mean ± SD and median (IQR) were calculated with Excel. A value of p below 0.05 was considered statistically significant.

3 | RESULTS

From May 2019 to September 2022, 72 patients were screened for the study. Two of them declined participation. Seventy patients were randomised in a laser:steroid ratio of 2:1, i.e. with 47 patients in the laser arm and 23 patients in the steroid arm. Three patients in the laser arm did not complete the 6-month visit, two because of pregnancy and one as a result of COVID-19 travel restrictions. One patient in the steroid arm wanted to stop participation before the 6-month visit. Forty-four women completed laser treatment and 6-month follow up, and 22 women completed steroid treatment and 6-month follow up (Figure 1). Seventeen patients (17/22, 77%)

used 0.05% topical clobetasol ointment and five patients (5/22, 23%) preferred 0.05% topical clobetasol cream. Only three patients needed an extra steroid treatment, but never on interval days during the first 2 months. All three used clobetasol ointment, two of them needed three extra treatments during the interval weeks, the third patient needed 14 extra treatments during months 3–6. The twice daily option was never used.

Seventy-one percent (47/66) of sequential eligible patients from our clinic were included, irrespective of their previous history, an additional 19.7% (13/66) were members of a LS support network actively asking for study participation and 9.1% (6/66) were referred to our clinic by general practitioners. The average age at baseline was 59.3 years (22–86 years), the mean body mass index was 25.6 kg/m^2, and the median parity was 2 (Table 1). Seventy-one percent were postmenopausal and 58% applied local estrogen. Twenty-nine percent were current or past smokers, 3% had diabetes. The median symptom duration was 5 years and 14% had a family history of LS. Sixty-one percent were allocated to the LSL group and 39% to the LSH group, and 55% had intercourse. None of these criteria differed significantly between the laser and steroid groups (Table 1). Of the 39% (26/66) with advanced disease (LSH; LS score ≥7), 96% (25/26) had severe agglutination of the labia, 50% (13/26) had severe introital stenosis and 100% (26/26) had severe atrophy, including vulvar architectural changes.

3.1 | Primary outcome

Laser therapy showed a significant improvement of the total LS score (−2.34 ± 1.20, 95% CI −2.71 to −1.98; $p < 0.001$, effect size 0.85) at 6 months compared with baseline, including improvements in the subcategories erosion ($p = 0.011$), hyperkeratosis ($p < 0.001$), fissures ($p = 0.005$) and atrophy, especially the skin quality ($p < 0.001$) (Table 2). Architectural changes such as agglutination ($p = 0.197$) and stenosis ($p = 0.467$) were not improved by laser therapy.

3.2 | Safety

Pain/discomfort during laser treatment was minor. Of the 44 laser group patients, five reported pain in laser session 1, three in session 2, five in session 3 and four in session 4. Corresponding peri-interventional VAS scores (0–10) were low. With a total of 176 (= 4 × 44) treatments, patients indicated no pain (VAS 0) 159 times, VAS 1 or 2 15 times, VAS 3 once and VAS 7 once. Routinely, no local anaesthetic was necessary even though treatment involved an ablative Er:YAG step. In only 4.5% (8/176) of all treatments were topical analgesics needed, never in in session 1, once in session 2, thrice in session 3, and four times in session 4. No serious adverse events related to the laser treatment were encountered, and complications were minor and transient. Within the first week after laser treatment, only 2.3% (4/176) reported adverse events: one urinary tract infection, two vulvar itching and one vulvar pain.

3.3 | LS score

Similar to the laser group, the steroid group also showed significant improvement of the total LS score (−0.95 ± 0.90, 95% CI −1.35 to −0.56; $p = 0.014$, effect size 0.78), including the subcategories erosion ($p = 0.003$), hyperkeratosis ($p = 0.035$) and fissures ($p = 0.046$), but not for agglutination ($p = 1.0$) and stenosis ($p = 1.0$) (Table 2). In contrast to the laser group, atrophy did not change, the skin remained dry and thin ($p = 0.317$). The 6-month outcome for atrophy was significantly different between the laser and steroid groups ($p < 0.001$).

3.4 | VAS symptom intensity

The characteristic vulvar symptoms, itching and burning, improved significantly for the laser group ($p < 0.001$; $p < 0.001$, respectively) and the steroid group ($p = 0.008$; $p = 0.012$, respectively) (Table 2). Unprovoked vulvar pain and pain at intercourse improved, but were not significant for both laser ($p = 0.052$; $p = 0.053$, respectively) and steroid ($p = 0.253$; $p = 0.088$, respectively) groups. The total VAS score (itching, burning and pain) evaluated for all 66 patients significantly improved for both the laser group ($p < 0.001$) and the steroid group ($p = 0.001$), without significant differences between the two groups.

3.5 | VSQ score

Vulvovaginal symptoms assessed by subjective VSQ questions 1–7 significantly improved for both laser ($p < 0.001$) and steroid ($p = 0.010$) arms (Table 2). The VSQ subcategories life impact (questions 12–16) and intercourse (questions 18–21) did not improve significantly for the laser ($p = 0.176$; $p = 0.275$, respectively) and steroid ($p = 0.229$; $p = 0.320$, respectively) groups. The subcategory VSQ emotions (questions 8–11) improved significantly for the laser group ($p = 0.011$), but not for the steroid group ($p = 0.180$). The total VSQ score (questions 1–16) evaluated for all 66 patients significantly improved for both the laser ($p < 0.001$) and steroid ($p = 0.043$) groups, without significant differences between the two groups.

The percentage of patients with a ≥50% improvement of VAS or VSQ scores at the 6-month follow up was similar in the laser and steroid groups. Laser versus steroid group comparisons for the total VAS score (itching, burning and pain) were 61% (27/44) versus 50% (11/22) with a ≥50% improvement, for VAS pain intercourse 48% (13/27) versus 44% (4/9), for VSQ questions 1–16 50% (22/44) versus 36% (8/22) and for VSQ

TABLE 2 Six-month outcomes LS score, VAS symptoms, VSQ.

Variable	Baseline, mean ± SD	Six months, mean ± SD	Change, mean ± SD	*p* value within
LS score total				
Laser ($n = 44$)[a]	6.27 ± 1.25	3.93 ± 1.34	−2.34 ± 1.20	**<0.001**
Steroid ($n = 22$)	6.05 ± 1.50	5.09 ± 1.15	−0.95 ± 0.90	**0.014**
p value between	0.391	**<0.001**	**<0.001**	
LS score erosions				
Laser ($n = 44$)	0.39 ± 0.58	0.09 ± 0.36	−0.30 ± 0.70	**0.011**
Steroid ($n = 22$)	0.41 ± 0.50	0.00 ± 0.00	−0.41 ± 0.50	**0.003**
p value between	0.698	0.214	0.444	
LS score hyperkeratosis				
Laser ($n = 44$)	0.80 ± 0.67	0.16 ± 0.37	−0.64 ± 0.69	**<0.001**
Steroid ($n = 22$)	0.64 ± 0.66	0.32 ± 0.48	−0.32 ± 0.48	**0.035**
p value between	0.351	0.139	0.073	
LS score fissures				
Laser ($n = 44$)	0.36 ± 0.49	0.07 ± 0.33	−0.30 ± 0.63	**0.005**
Steroid ($n = 22$)	0.18 ± 0.39	0.00 ± 0.00	−0.18 ± 0.39	**0.046**
p value between	0.133	0.314	0.247	
LS score agglutination				
Laser ($n = 44$)	1.70 ± 0.46	1.59 ± 0.50	−0.11 ± 0.32	0.197
Steroid ($n = 22$)	1.73 ± 0.46	1.73 ± 0.46	0.00 ± 0.00	1
p value between	0.849	0.281	0.103	
LS score stenosis				
Laser ($n = 44$)	1.02 ± 0.59	0.95 ± 0.53	−0.07 ± 0.25	0.467
Steroid ($n = 22$)	1.09 ± 0.68	1.09 ± 0.68	0.00 ± 0.00	1
p value between	0.659	0.69	0.213	
LS score atrophy				
Laser ($n = 44$)	2.00 ± 0.00	1.07 ± 0.50	−0.93 ± 0.50	**<0.001**
Steroid ($n = 22$)	2.00 ± 0.00	1.95 ± 0.21	−0.05 ± 0.21	0.317
p value between	1	**<0.001**	**<0.001**	
VAS total (itching, burning, pain)				
Laser ($n = 44$)	11.59 ± 6.87	5.75 ± 6.50	−5.84 ± 6.19	**<0.001**
Steroid ($n = 22$)	9.36 ± 5.60	4.00 ± 3.12	−5.36 ± 6.33	**0.001**
p value between	0.303	0.647	0.881	
VAS itching				
Laser ($n = 44$)	5.50 ± 2.62	2.61 ± 2.49	−2.89 ± 2.56	**<0.001**
Steroid ($n = 22$)	4.36 ± 3.08	2.00 ± 1.45	−2.36 ± 3.36	**0.008**
p value between	0.153	0.609	0.331	
VAS burning				
Laser ($n = 44$)	3.91 ± 2.87	2.00 ± 2.44	−1.91 ± 2.86	**<0.001**
Steroid ($n = 22$)	3.77 ± 2.86	1.55 ± 1.71	−2.23 ± 3.39	**0.012**
p value between	0.995	0.747	0.727	
VAS pain				
Laser ($n = 44$)	2.18 ± 2.93	1.14 ± 2.18	−1.05 ± 2.48	0.052
Steroid ($n = 22$)	1.23 ± 2.47	0.45 ± 1.18	−0.77 ± 1.95	0.253
p value between	0.152	0.265	0.747	
VAS pain intercourse				
Laser ($n = 27$)	5.00 ± 3.29	3.26 ± 3.13	−1.74 ± 2.36	0.053

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TABLE 2 (Continued)

Variable	Baseline, mean ± SD	Six months, mean ± SD	Change, mean ± SD	*p* value within
Steroid ($n = 9$)	4.00 ± 2.35	2.22 ± 2.22	−1.78 ± 1.39	0.088
p value between	0.408	0.419	0.697	
VSQ total (Q1–16)				
Laser ($n = 44$)	8.11 ± 3.58	4.89 ± 4.42	−3.23 ± 3.21	**<0.001**
Steroid ($n = 22$)	7.68 ± 3.20	5.36 ± 4.27	−2.32 ± 3.43	**0.043**
p value between	0.473	0.637	0.408	
VSQ symptoms (Q1–7)				
Laser ($n = 44$)	4.32 ± 1.72	2.41 ± 1.93	−1.91 ± 2.37	**<0.001**
Steroid ($n = 22$)	3.82 ± 1.68	2.59 ± 1.53	−1.23 ± 1.69	**0.010**
p value between	0.153	0.586	0.216	
VSQ emotions (Q8–11)				
Laser ($n = 44$)	2.07 ± 1.62	1.20 ± 1.56	−0.86 ± 1.41	**0.011**
Steroid ($n = 22$)	2.14 ± 1.58	1.45 ± 1.65	−0.68 ± 1.55	0.180
p value between	0.922	0.498	0.431	
VSQ life impact (Q12–16)				
Laser ($n = 44$)	1.73 ± 1.80	1.27 ± 1.81	−0.45 ± 1.02	0.176
Steroid ($n = 22$)	1.73 ± 1.80	1.32 ± 1.81	−0.41 ± 1.59	0.229
p value between	0.785	0.808	1	
VSQ intercourse (Q18–21)				
Laser ($n = 27$)	2.44 ± 1.28	2.00 ± 1.47	−0.44 ± 1.05	0.275
Steroid ($n = 9$)	2.56 ± 1.33	2.00 ± 1.32	−0.56 ± 0.73	0.320
p value between	0.777	0.955	0.722	

[a]Primary outcome; LS score: clinical lichen sclerosus score; VAS: visual analogue scale (0–10); VSQ: vulvovaginal symptoms questionnaire; Q1–21: specific questions of the VSQ.
Note: Grey shades highlight the total of the LS scores (erosions, hyperkeratosis, fissures, agglutination, stenosis, atrophy), the total of the VAS scores for itching, burning and pain, and the total of the VSQ scores for VSQ questions 1–16, respectively. Statistically significant values are shown in bold.

intercourse (questions 18–21) 30% (8/27) versus 22% (2/9). The differences between the study arms were not significant.

3.6 | Patient satisfaction (PGI-I)

Overall, more patients felt better after laser treatment than after steroid therapy. At 6 months, 32% (14/44) of the laser group and 4.5% (1/22) of the steroid group felt very much better, 32% (14/44) and 41% (9/22) felt much better, and 27% (12/44) and 36% (8/22) felt a little better than before the interventions, respectively. Hence, only 9.0% (4/44) and 18.5% (4/22) experienced no change or worsening after the therapies, respectively. These differences between the laser and steroid arms were significant ($p = 0.035$).

4 | DISCUSSION

4.1 | Main findings

In women with clinically diagnosed LS, dual Nd:YAG/Er:YAG laser treatment significantly improved the clinical LS score and subjective parameters at the 6-month visit. The laser therapy was safe, generally painless, and without serious adverse events. The outcomes for atrophy and treatment satisfaction were significantly better in the laser arm than in the steroid arm, but all other improvements were similar in both arms.

4.2 | Strengths and limitations

One major strength of this study is the randomised controlled design with the current recommended first-line therapy with steroid as the active comparator. The number of patients was equal or higher than in published RCTs on LS.[5,9–13] Another strength is the high adherence to both treatment arms. This reflects that treatments in both arms were well tolerated. We also think that the study design contributed to the high patient compliance. Patients preferred participating in a study with two active arms rather than receiving a placebo/sham treatment, and the individualised, single-site study setting with frequent study visits additionally supported study adherence.

The lack of sham treatment and, consequently, the lack of blinding were study limitations. Patients might have a positive attitude towards the new laser therapy already before starting with their first treatment, particularly those who

actively asked for study participation. Well-informed patients apply steroids correctly and in general, experience the benefit of steroids. Nevertheless, certain patients might still have an aversion or scepticism towards steroids. Moreover, three or four laser treatments might be more convenient than daily applications of local corticosteroids. All these subjective attitudes could lead to a study bias favouring laser therapy.

Experience from treating stress urinary incontinence (SUI) showed that intravaginal laser therapy could cure mild and moderate SUI, but not severe SUI stage III.[30] Therefore, a similar dual stratification was used to equally assign high and low LS severity grades (LSH/LSL) to the two study arms. The stratification helped to avoid a bias for an uneven distribution.

The reasoning for using the interval steroid therapy rather than the internationally recommended daily application treatment scheme was to avoid tachyphylaxis and rebound effects.[1,2,4] Patients, however, were allowed to increase the clobetasol treatment when subjectively needed. Nevertheless, this option was used only exceptionally. This suggests that our steroid regimen was largely sufficient to control LS symptoms, although this lower dose scheme may represent a possible study limitation.

The short follow up of 2 months after laser therapy could be interpreted as a study limitation. However, as we analysed a novel treatment technique—at time of study initiation in 2019 without precedent nor previous data on efficacy and side effects—we chose a timely evaluation. This was similar to other studies,[5,10,11] and allowed the interpretation/comparison of unambiguous laser versus steroid effects without influence of crossover treatments.

4.3 | Interpretation

Most studies to treat vulvar LS have used the fractional-ablative CO_2 laser,[6–9,31] one used a fractional-ablative Er:YAG laser[32] and one—similar to this study—the non-ablative Nd:YAG laser.[5] With the fractional ablative laser settings, heat penetrates into deep tissue layers via microchannels created by the laser. This activates neocollagenesis and neovascularisation and improves epithelial trophism.[21] Long Nd:YAG laser pulses also generate heat in deep cell layers and induce similar tissue regeneration.[14] As the wavelength of the Nd:YAG laser is not absorbed by water, the laser beam penetrates without surface tissue damage (>5 mm). Therefore, in contrast to the CO_2 laser,[9,11,12] the non-ablative Nd:YAG laser treatment of the vulva is less painful. It only required the administration of topical anaesthetics in 4.5% of all treatments. Consequently, the recovery time after Nd:YAG laser treatment was shorter, approximately 1 day versus almost 1 week after CO_2 laser therapy.

In our study, the dual Nd:YAG/Er:YAG laser treatment was safe and efficient, which was in agreement with other vulvovaginal laser treatments of LS.[8] Four previously published RCTs also compared laser and topical steroid, three of them used the CO_2 laser,[9,11,12] and one used the Nd:YAG laser.[5] Two RCTs compared CO_2 with placebo/sham or 'low-dose' CO_2 laser.[10,13] All RCTs showed subjective improvement after laser therapy, independent of the type of laser. Furthermore, improvement after laser therapy was significantly better than after steroid therapy.[5,9,11] In one study, histology data did not improve after laser nor after sham therapy and there was no difference between the study arms,[10] and in another study, high- and low-dose laser therapy led to improvement without difference between the study arms.[13]

In this study, laser therapy, but not steroid therapy, improved vulvar skin quality. Similarly, another RCT also showed improved skin elasticity and skin colour after laser but not after steroid therapy.[11] In another study investigating genitourinary syndrome of menopause, vulvar laser treatment led to a major improvement of the vulvar health index that—among other criteria—also evaluates vulvar skin colour and elasticity.[21] In our study, more patients felt very much/much better (64%) after laser than after steroid therapy (45%). These findings are in accordance with other studies, where patients were more satisfied after laser treatment compared with steroid therapy.[5,9,12]

5 | CONCLUSION

The novel dual Nd:YAG/Er:YAG laser therapy for vulvar LS showed similar improvement of symptoms, but better skin quality and therapy satisfaction than after the treatment with high-potency topical steroids. Therefore, this controlled, outpatient, minimally invasive laser treatment offers good insights with potential to influence clinical practice. An unknown risk of disease progression still remains. Regular check-ups and longer post-treatment observation periods are necessary.

AUTHOR CONTRIBUTIONS

IZ contributed to conceptualisation, planning, patient treatment, organisation of study visits, data acquisition, review of manuscript; MG contributed to conceptualisation, planning, data analysis, original draft writing, review and editing; DF contributed to data acquisition, data curation, data analysis, statistics, review of manuscript; CW contributed to conceptualisation, planning, randomisation, ethics application, statistics, review of manuscript; SR contributed to conceptualisation, review of manuscript; VV contributed to conceptualisation, planning, data analysis, supervision, manuscript writing, review of manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The trial protocol was approved on 15 April 2019 by the ethics committee of Eastern Switzerland (EKOS 19/056, BASEC-ID: 2019-00634), and was registered at clinicaltrials.gov (NCT03926299).

ORCID

Marianne Gamper https://orcid.org/0000-0002-8235-1239
Sigrid Regauer https://orcid.org/0000-0002-7077-578X
Volker Viereck https://orcid.org/0000-0002-1116-8912

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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