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CO_2 non-ablative laser versus topical clobetasol for lichen sclerosus: a prospective, open-label, randomized trial

Version 3

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Study code: LASER-LICH1

ClinicalTrials.gov registration: NCT05010421

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1. Background

Lichen sclerosus (LS) is a common autoimmune disorder of the genital skin. It affects 1/900 women with an age peak in the sixth decade of life [1]. LS is a chronic inflammatory condition affecting the genital, perineal, and perianal areas and causes itching, burning, pain, and soreness. Histologically, LS is characterized by epidermal atrophy, hyperkeratosis, follicular plugging, degeneration of the basal layer, and subepidermal hyalinization of collagen in the papillary dermis with a lymphocytic infiltrate [2]. Affected women typically suffer significant long-term genital damage including scarring, fusion of the vulval labia, narrowing of the vaginal opening, dyspareunia, and burying of the clitoris [1, 3]. In addition, LS is associated with an increased risk of vulvar cancer [3].

Treatment options of LS include topical steroids such as clobetasol [3], topical immunomodulators such as tacrolimus [4], and non-ablative laser treatment [5]. In a systematic review of the literature with 7 studies and 249 participants, clobetasol achieved improvement rates and remission rates of 70% to 89% and 20% to 35%, respectively [6]. In comparison, non-ablative laser treatment leads to significant improvements in vulvar itching, dryness, pain, and dyspareunia in 50% to 85% of women [7–11] with remission rates of up to 80% after 14 years of follow-up [12]. Although both treatments are well documented and used in clinical practice, direct comparative studies assessing the efficacy of topical corticosteroids versus laser treatment in women with LS are rare. For example, in a PubMed literature search (search date 2021-03-14; search terms: lichen sclerosus, laser, corticosteroids, steroids, clobetasol, randomized) only one randomized trial was identified [13]. In this study, Bizjak Ogrinc et al. included 40 women with LS and compared 3 applications of non-ablative laser 2 weeks apart with 4 weeks of twice daily (2 weeks), once daily (1 week), and every other day (1 week) of topical clobetasol 0.05% cream. After 3 months of treatment laser-treated women had a significantly higher sum score (including burning, itching, and pain) measured on an 11-step visual analogue scale (VAS). Both treatments demonstrated histological improvement with reductions of inflammatory hallmarks in skin biopsies.

Given this body of evidence, more high-quality studies are needed to define the superiority/inferiority of the different available treatment options such as non-ablative laser and topical corticosteroids. Therefore, we intend to conduct a prospective, randomized trial comparing non-ablative CO_2 laser treatment and topical clobetasol 0.05%. The aim of this prospective, randomized, open-label, comparative trial is to establish or refute the superiority of 3 courses of non-ablative treatment by CO_2 laser every 14 days compared to topical clobetasol 0.05% 3 times/week for 3 months. The primary endpoint of this study is a sum score including the pathognomonic symptoms of LS, namely vulvar burning, itching, and pain, each measured on an 11-step VAS. Secondary endpoints will include the physician-scored rate of visual improvement (measured on an 11-item VAS), side effects, and patient-reported outcomes such as subjective overall improvement, general satisfaction, and quality of life (measured by a validated questionnaire for vulval disorders; i.e. the VDQI (Vulval Disease Quality of Life Index; see Annex 1) [14].

2. Study objectives

2.1. Primary study objective

The primary study objective is a summary score of three symptoms of LS, i.e. vulvar burning, itching, and pain, each measured on an 11-step VAS (min 0; max 30).

2.2. Secondary study objectives

Efficacy

- The physician-scored rate of visual improvement (measured on an 11-item VAS after 3 months)

Safety

- Side effects (perioperative and postoperative complications up to 7 days) including but not limited to bleeding, infection, wound breakdown, unscheduled re-admission, and local pain necessitating systemic analgesia

Patient-reported outcomes

- Subjective overall improvement (measured on an 11-item VAS after 3 months)
- Quality of life (QoL) assessed before the start of therapy and after every treatment course (laser group) or every 3 weeks (clobetasol group) using a standardized, validated questionnaire (VDQI) [14]

3. Methodology

This study is a prospective, randomized, open-label, comparative clinical trial testing the superiority of 3 courses of non-ablative CO_2 laser treatment every 14 days compared to topical clobetasol 0.05% daily for 1 month, followed by every other day for 1 month, followed by 3 times per week for 1 month with superiority defined as a significantly lower local symptom sum score.

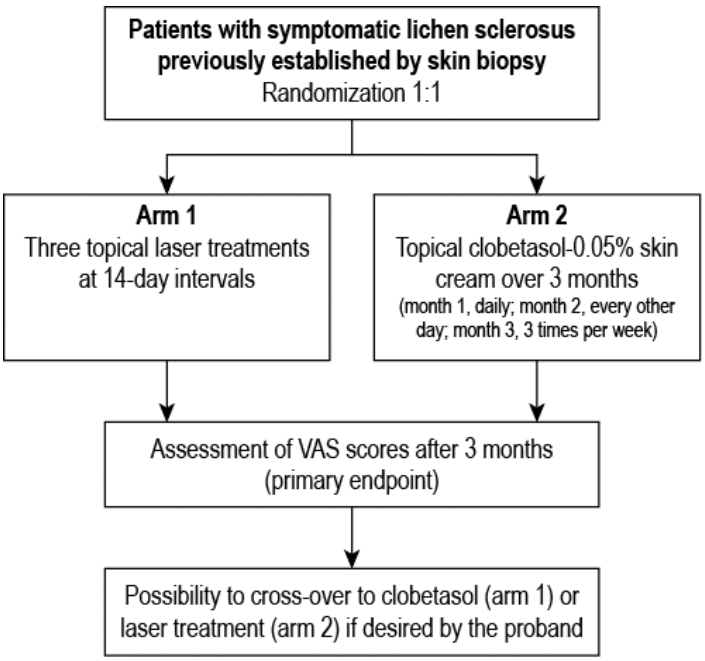

Figure 1. Study algorithm

3.1. Study endpoints

Subjective improvement (primary endpoint)

The primary study objective will be subjective improvement of symptoms typically associated with LS measured by a summary score of the following three symptoms of LS: 1) vulvar burning, 2) vulvar itching, and 3) vulvar pain, each measured on an 11-step VAS, for a minimum total score of 0 and a maximum total score of 30. Assessment will be after 3 months starting from the day of the first laser treatment (arm 1) or the first day of clobetasol application (arm 2).

Efficacy – Visual Improvement

Efficacy will be measured by the physician-scored rate of visual improvement (measured on an 11-step VAS after 3 months). Visual improvement is defined as a mean lower VAS by at least 3 steps comparing the physician-scored VAS at study entry with the physician-scored VAS after 3 months.

Safety

Safety assessments will include predefined treatment-associated side effects including perioperative and postoperative (for up to 7 days) complications such as wound bleeding, wound infection, wound breakdown, unscheduled re-admission, and local pain necessitating systemic analgesia. These items will be recorded during and after surgery (in arm 1) and will be collected by telephone interview 7 days after treatment start (in both arms).

Patient Reported Outcomes (PROs)

PROs will include subjective overall improvement as measured by an 11-item VAS after 3 months and a standardized, validated questionnaire (VDQI) which are administered before the start of therapy and after every treatment course (arm 1) or after 3 and 7 weeks (arm 2).

3.2. Study population

LASER-LICH1 will include women with an established diagnosis of LS (confirmed by a previous or actual skin biopsy demonstrating a histological diagnosis of LS by pathologist assessment).

Inclusion criteria

- Women, age ≥ 18 years
- Established diagnosis of LS (vulva and/or perineum and/or perianal region)
- Willingness to comply with study requirements
- No significant language barrier

Exclusion criteria

- Concurrent immunosuppressive treatment
- A history of vulvar cancer and/or vulvar dysplasia
- A history of vulvar surgery
- A contraindication against clobetasol treatment

- A known sun light allergy
- A known skin condition interfering with local ablative treatment such as neurodermatitis or bullous pemphigoid

3.3. Randomization

Randomization is performed using a computer-generated randomization list (block size 4, 6) [15]. The randomization schedule (indexed by consecutive numbers) is uploaded to REDCap (see 5.1.), where it is not visible to anyone. After recruitment and documentation of the initial visit, patients are allocated to a treatment group by pressing the "Randomize" button provided by REDCap's randomization module. In case of electronics failure, randomization can be performed by opening the correspondingly numbered (next consecutive randomization index) sealed envelope that contains treatment allocation.

3.4. Study procedures

Both arms

Vulvar biopsy and photography at study entry and after 3 months of treatment, as well as assessment of the Vulvar Disease Quality of Life Index (VDQI) and symptoms questionnaire.

Arm 1 (CO_2 non-ablative laser treatment)

Women randomized to study arm 1 will undergo 3 applications every 14 days of a superficial, non-ablative laser treatment of affected vulvar skin areas using a non-ablative CO_2 laser (AcuPulse™ 30W CO_2 laser system with SurgyTouch scanner and FemTouch kit, Lumenis, Dreieich, Germany) with a R33 non-contact hand piece with a 9-mm spot size, Piano pulse mode (5 seconds), and 90 J/cm^2 fluence. Six passes are being performed over the affected whitish or reddened areas and borderline granulations. These parameters and application details follow the instructions previously recommended for LS treatment [13].

Arm 2 (clobetasol-0.05% Cream)

Women randomized to study arm 2 will undergo treatment of the affected vulvar skin areas with topical clobetasol 0.05% daily for 1 month, followed by every other day for 1 month, followed by 3 times per week for 1 month. Treatment will be applied by probands. On the clobetasol-free days, patients will be advised to use a topical skin care moisturizer such as Deumavan Natur Salbe®, an inert, non-medical, non-prescription skin care ointment containing paraffinum liquidum, petrolatum, paraffin, and vitamin E.

Patients in arms 1 and 2 are treated and assessed as outlined in Table 1.

Table 1. Study procedures at different time points in both study arms

Timepoint	Arm 1 (laser treatment)	Arm 2 (clobetasol treatment)
Day -3 to -7	Initial assessment VDQI and symptoms questionnaire Photography Biopsy Randomization	Same as arm 1
Day 0 - Treatment start	First laser treatment	Start of clobetasol treatment
Day 14	VDQI and symptoms questionnaire Photography Second laser treatment	VDQI and symptoms questionnaire Side effects questionnaire (via telephone interview or online)
Day 28	VDQI and symptoms questionnaire Photography Third laser treatment	-
Day 42 (by telephone)	VDQI and symptoms questionnaire Side effects questionnaire	Same as arm 1
After 3 months (follow up visit)	VDQI and symptoms questionnaire Physician assessment Photography Cross-over optional	Same as arm 1
After 6 months (follow up visit for cross-over patients)	VDQI and symptoms questionnaire Physician assessment	Same as arm 1

VDQI, Vulval Disease Quality of Life Index

3.5. Number of study participants, sample size calculation

198 women will be recruited for this study (99 per study arm). The sample size was calculated based on the study hypothesis that laser treatment of LS compared to topical clobetasol will lead to a 3 steps higher sum score on an 11-step VAS including 3 items (itching, burning, pain) with a minimum score of 0 and a maximum score of 30 and an estimated mean score of 12 and a standard deviation of 4 [13]. With a sample size of 180 participants, the study has a power of >90% to detect difference of 2 VAS steps with a standard deviation of ±4 and a level of significance of 0.05 using a nonparametric test such as the Mann-Whitney U test. Assuming a 10% drop out rate after randomization, we aim to recruit 198 patients. A difference of at least 2 VAS steps was assumed to be clinically relevant based on our previous experience [16–18].

3.6. Study duration

Study duration will be 2 years from first patient in to last patient out. With an estimated total of 6-8 women with LS per week seen in the outpatient clinic of the study site and estimating a recruitment percentage of 50%, 2 years will be needed to recruit 198 probands.

3.7. Study site

This study will be a monocentric clinical trial with the study site being located at the Department of Obstetrics & Gynecology, Ruhr-Universität Bochum, Marien Hospital Herne, Hölkeskampring 40, 44625 Herne, Germany (phone: +49 2323 499 1801, fax: +49 2323 499 3393; website: https://www.marienhospital-herne.de).

4. Risk-benefit assessment

- **Benefits**
  Probands in both study arm will be treated with a well-established and effective treatment regimen in line with clinical practice. If the study hypothesis is confirmed, probands in arm 1 will be treated with a more effective treatment as indicated in a small randomized trial [13]. In order to ensure compliance and follow-up adherence, all probands in arm 2 will be offered laser treatment after 3 months in case they are not satisfied with clobetasol treatment. Likewise, all probands in arm 1 will be offered clobetasol treatment in case they are not satisfied with laser treatment.
- **Risks**
  The risks associated with both treatments are well described in the literature and are limited in frequency and severity. The most common complications of laser treatment include wound infection, scarring, and local pain in <10% of patients [7–13]. Corticosteroid treatment of the vulva is associated with thinning of the skin, epithelial disruption, and an increased risk of infection [3, 6].

In summary, the risk-benefit-ratio of this study is acceptable for probands in both study arms. In addition, we will offer all patients randomized into arm 1 to undergo laser treatment after the end of the study in case they are not satisfied with clobetasol treatment.

5. Data management

5.1. Data collection and data protection

Relevant patient data (from examinations, questionnaires, medical records) will be entered into a study database. For statistical analysis of the data, they will be exported from the database anonymously (i.e., without identifying data). Only the personnel entrusted with conducting the study have access to the data in the study database, which is ensured by personalized logins (user name, password) and access rights (roles) limited to the performance of the respective function. Study data will be collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based application designed to support data capture for research studies [19].

Data will not be passed on to third parties. The confidentiality of personal data is also guaranteed in any publications of the study results. The study database as well as the patient consents remain in the possession of the principal

investigator after completion of the study and are kept for at least 5 years after publication of the study or as long as required by legal regulations (for medical data at least 30 years).

The data collection schedule is shown in Annex 2. The complete case report form is in the "LASER-LICH1 Codebook" file.

5.2. Statistical analyses

Descriptive statistics will be used to report results. Data will be reported as numbers and proportions for categorical data, and means ± standard deviations or medians (interquartile ranges) for continuous data passing or failing the Shapiro-Wilk normality test, respectively. To compare groups, appropriate statistical tests will be employed (t-test/ANOVA or Mann-Whitney U test/ANOVA on ranks for continuous data; Chi square test or Fisher's exact test in case of small counts for proportions). All P-values will be two-tailed and a value <0.05 will be considered statistically significant. We will also perform multivariate logistic regression analyses with VAS score results as the dependent variable and study group, age, body mass index, smoking, and previous duration of LS (from first diagnosis of LS to study entry) as the independent variables. SigmaPlot 14.5 (Systat Software Inc., San Jose, CA) will be used to perform statistical calculations and to prepare graphs.

6. References

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Annex 1

Vulval Disease Quality of Life (VDQI) Fragebogen

1. Behandlung

a. Wie stark hat Sie die Behandlung Ihrer Vulva-Erkrankung während des letzten Monats beeinträchtigt?
Sehr stark (3) – Stark (2) – Gering (1) – Gar nicht (0)

2. Symptome

a. Wie stark ausgeprägt waren während des letzten Monats Juckreiz und/oder Brennen im Bereich der Vulva?
Sehr stark (3) – Stark (2) – Gering (1) – Gar nicht (0)

b. Wie oft fühlten Sie während des letzten Monats eine oder mehrere der folgenden Beschwerden: Schmerzen beim Wasserlassen, Schmerzen beim Geschlechtsverkehr, Hitzeempfindlichkeit, Ausfluß?
Sehr oft (3) – Oft (2) – Selten (1) – Nie (0)

3. **Empfinden**

a. Wie unangenehm oder peinlich waren Ihnen während des letzten Monats Ihre Vulva-Beschwerden?
Sehr unangenehm (3) – Unangenehm (2) – Wenig unangenehm (1) – Gar nicht unangenehm (0)

b. Wie stark wurde während des letzten Monats Ihr Körperbild (Weiblichkeit, Gefühl anders zu sein, Gefühl körperlich beeinträchtigt zu sein) durch Ihre Vulva-Beschwerden beeinträchtigt?
Sehr stark (3) – Stark (2) – Gering (1) – Gar nicht (0)

c. Wie stark fühlten Sie sich während des letzten Monats durch Ihre Vulva-Beschwerden gestresst oder ängstlich?
Sehr stark (3) – Stark (2) – Gering (1) – Gar nicht (0)

4. **Aktivitäten**

a. Wie häufig wurde während des letzten Monats die Wahl Ihrer Kleidung (Unterwäsche, Hosen, enge Kleidung, etc.) durch Ihre Vulva-Beschwerden beeinträchtigt?
Sehr häufig (3) – Häufig (2) – Selten (1) – Nie (0)

b. Wie stark wurde während des letzten Monats Ihr Nachtschlaf durch Ihre Vulva-Beschwerden beeinträchtigt?
Sehr stark (3) – Stark (2) – Gering (1) – Gar nicht (0)

c. Wie häufig wurden während des letzten Monats Ihre Freizeitaktivitäten (Einkaufen, Bummeln, Familienausflüge, Besuche, etc.) durch Ihre Vulva-Beschwerden beeinträchtigt?
Sehr häufig (3) – Häufig (2) – Selten (1) – Nie (0)

d. Wie häufig wurden während des letzten Monats Ihre Sozialkontakte (Freunde treffen, gemeinsame Spaziergänge, kulturelle Aktivitäten, Sport, etc.) durch Ihre Vulva-Beschwerden beeinträchtigt?
Sehr häufig (3) – Häufig (2) – Selten (1) – Nie (0)

e. Wie häufig wurden während des letzten Monats Ihre beruflichen Aktivitäten durch Ihre Vulva-Beschwerden beeinträchtigt?
Sehr häufig (3) – Häufig (2) – Selten (1) – Nie (0)

5. Beziehung/Sexualität

a. Wie stark wurde während des letzten Monats Ihre Partnerschaft durch Ihre Vulva-Beschwerden beeinträchtigt?
Sehr stark (3) – Stark (2) – Gering (1) – Gar nicht (0)

b. Wie stark wurde während des letzten Monats Ihr Sexualleben (Lust auf Sex, Häufigkeit des Geschlechtsverkehrs, Freude an Sex) durch Ihre Vulva-Beschwerden beeinträchtigt?
Sehr stark (3) – Stark (2) – Gering (1) – Gar nicht (0)

c. Wie häufig fühlten Sie sich während des letzten Monats aufgrund Ihre Vulva-Beschwerden hinsichtlich Ihres Sexuallebens gestresst und/oder verängstigt?
Sehr häufig (3) – Häufig (2) – Selten (1) – Nie (0)

6. Allgemeine Gesundheit

a. Wie häufig machten Sie sich während des letzten Monats Sorgen über Langzeitfolgen Ihrer Vulva-Beschwerden (wie z.B. Krebs, Behinderung, Pflegebedürftigkeit, etc.)?
Sehr häufig (3) – Häufig (2) – Selten (1) – Nie (0)

Maximale Punktezahl: 45

Annex 2

Case Report Form (REDCap)

Table 2. Data collection schedule

Data Collection Instrument	Rekrutierung	Untersuchung	T0	T14	T28	T42	T90	T180
Stammdaten	●							
Einwilligung	●							
Anamnese (survey)	●							
Symptomfragebogen (survey)	●			●	●	●	●	●
VDQI Fragebogen (survey)	●			●	●	●	●	●
Fotografie (survey)		●		●	●		●	●
Biopsie		●					●	
Pathologiebericht		●					●	
Randomisierung	●							
Laser-Behandlung			●	●	●			
Clobetasol-Behandlung			●					
Komplikationen			●	●	●	●		
Arztbeurteilung							●	●
Cross-Over	●							
Sonstiger Kontakt	●							
Vorzeitige Beendigung bzw. Widerruf	●							

Some instruments apply only to one arm of the study. See Table 1 (chapter 3.4) for details.

Individual items in the data collection instruments are described in the file “LASER-LICH1 Codebook”. A printout of the (electronic) forms is available in the file “LASER-LICH1 CRF”.