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Full length article

LASER treatment in gynaecology –A randomized controlled trial in women with symptomatic lichen sclerosus

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ABSTRACT

Objective: Aim of our study was to evaluate the therapeutic effect of laser treatment in vulvar lichen sclerosus, mainly the reduction of existing symptoms as itching, burning and pain. We asked about the different outcome by using different application doses.

Study design: We conducted a prospective randomized double-blind dose-controlled trial in our dysplasia unit specializing vulvar disorders. 67patients with active LS were included. LS was confirmed by biopsy or by the validated CSS (clinical scoring system of vulvar LS). Computer generated randomization resulted in two groups, each group received a different application dose.(LDG- low dose group, NDG- normal dose group) During the study period of 18 weeks all participants received three laser applications in three subsequent sessions of three weeks. Two follow-ups six and twelve weeks after the first application was performed. At every visit, the participants filled in the VAS (visual analogue scale) for recording the actual vulvar symptoms as itching burning or pain on a range from 0 to 10.

Results: Before treatment the mean VAS-Score was 4.3 (STD ± 2.4) in the NDG and 5.1(±2.6) in the LDG. After 18 weeks, the mean reduction was −2.4 (±2.3) for NDG and −2.7 (±2.8) for LDG. Four patients (two of each group) reported more pain after than before treatment. Both groups show significant lower VAS-Scores 18 weeks after the treatment than before therapy ($p < 0.0001$).

The reduction of symptoms after 18 weeks between NDG and LDG was not significant ($p = 0.6244$).

Conclusion: Laser treatment with the microablative CO2 laser leads to a significant improvement for symptoms of LS.

A higher dosage of laser radiation shows no benefit concerning the symptoms. We have not observed any serious adverse events during this study.

Introduction

Lichen sclerosus (LS) is a chronical inflammatory progressive dermatosis affecting the skin. Disseminate, thin, porcelain-white plaques may be presented, accompanied by purpura, hyperkeratosis, fissures, erosions or ulcerations [1].Widespread lesions may affect the anogenital area, but in few cases extragenital lesions can also be seen. Advanced LS has the risk of and developing precursor lesions for intraepithelial neoplasia (dVIN) and squamous cell vulvar carcinoma [2–3]. Four to seven percent of the women with LS may develop a vulvar carcinoma (Fig. 1).

The diagnosis for LS is a clinical diagnosis according the validated CSS (clinical scoring system) [4] of vulvar LS. A biopsy is not mandatory, except for cases with doubtful clinical presentation or dysplasia that has to be excluded (Fig. 2).

Histopathological diagnosis in early LS is a challenge [5,6] and may possibly lead to a discrepancy between the clinical picture and histopathological results [5].

Gold standard in therapy of LS is the application of potent or ultrapotent topical corticosteroids as Clobetasol, but in many cases the clinical signs of LS are not optimally repressed, despite of adequate amount of corticosteroids that are applied.Therapy requires long-term compliance of the patients and is occasionally refractory concerning the therapeutic effect. Additionally, overuse of Clobetasol may be

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deleterious for the skin. A recent cross sectional study in patients with dermatophytosis noted that steroid abuse happened in 92% of patients with hypopigmentation, striae, teleangiectasia and atrophy as consequence [7].

The need for a second line therapy is obvious such as topical calcineurin inhibitors, oral or topical retinoids, and immunosuppressors [8].

Another promising alternative may be the local application of laser therapy.

Meanwhile the use of fractionated ablative carbon dioxide (CO_2) laser application indicates a new option in alternative treatment in LS. The application of tiny laser spots spacing 1000 μm allows a superficial ablative effect of the treated tissue. Microablation stimulates the remodeling of the connected tissue and provokes an ultrastructural modification of the dermis [9].

Several publications show the described effects [9–12].

A recent systematic review [13] identified many limitations of previously published studies involving that only three out of 24 included studies were published in peer reviewed journals. Only two had a prospectively published protocol and follow-up was shorter than 12 weeks, which is the recommended duration of treatment, studies were underpowered and seven out of 24 were commercially funded implying bias, eleven did not include conflict of interests.

The aim of the study was the effect of an appropriate dose CO2 laser therapy on bothersome symptoms in women with LS compared to a low dose of laser that could be considered a placebo or sham therapy.

As we knew from prior treatments, a true placebo or sham treatment was not possible due to acoustic and visible signals that the laser produces during treatment. This could possibly lead to unblinding of the patients. For this reason we chose a very low dose laser therapy that we considered to be too low dose to cause any effects.

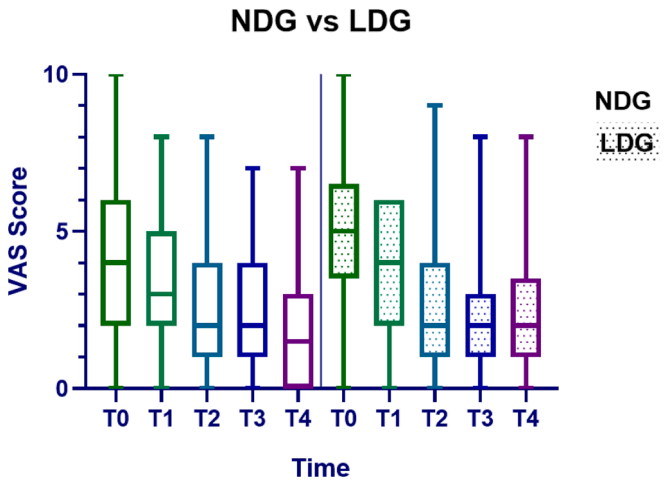

Fig. 2. VAS Score before and after treatment; NDG: normal dose group, LDG = low dose group.

Material and methods

We performed the current study in our tertiary referral dysplasia unit specialized in vulvar dysplasia in in the University Women's Hospital Bern, Inselspital, Switzerland, between 1/ 2020 and 1/2022.

The study was prospectively registered at the Swiss National Clinical

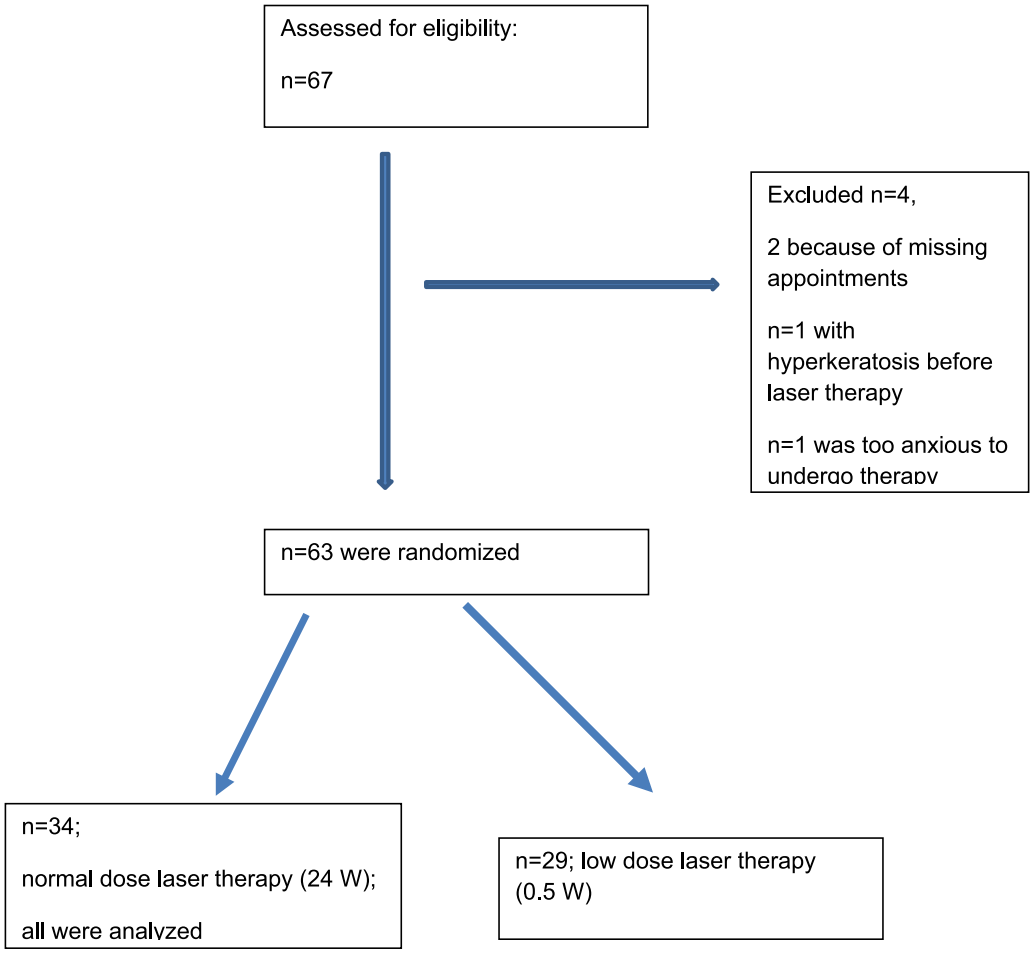

Fig. 1. CONSORT diagram.

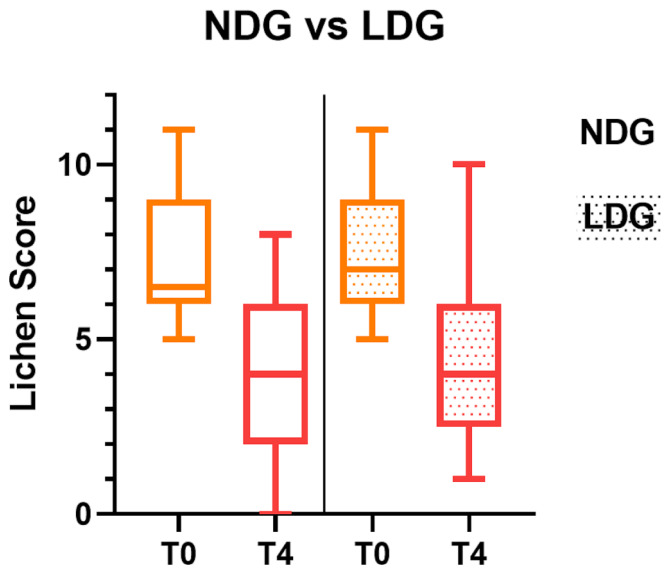

Fig. 3.

trial Portal (SNCTP via BASEC; SNCTP 000003817, BASEC 2019-01524, changed 29.04.2022).

Ethical consent from the local ethics committee was obtained (Kantonale Ethikkommission Bern, 11/2020) and Swiss medic (Medical Devices Clinical Investigations) approved the study (Ref.10000575; 10/2020).

Randomization was computer generated, using "Research Randomizer", version 1997–2019 by Geoffrey C. Urbaniak and Scott Plous in order to randomize the order patients to the two groups in a ratio 1:1. Participants were randomized in either normal dosed group and low dosed group. Randomization consisted of three steps: generation of the random allocation sequence, allocation concealment, and implementation of the random allocation sequence using a computer based fixed allocation system that was concealed to the patients to ensure blinding. Blinding of the investigator was not possible to the necessity of defining the laser settings.

The same clinician performed the laser treatment in all patients (EK).

Primary objective was the change of symptom bother as continuous measure as determined by VAS (visual analogue scale) from 0 = no bother to 10 = the worst bother I can imagine asking the patient the question "How is your current bother in the vulva region? (13).

Secondary outcome were the changes of the lichen score [4] before and after treatment and quality of life and sexual function as determined by a non-validated questionnaire.

All participants suffered from genital LS, which was confirmed by biopsy or by the validated clinical scoring system of vulvar LS [4].

Exclusion criteria were pregnancy, local bacterial, fungal or parasitical infection as determined by native microscopy, other severe dermatoses except of LS, vulvar cancer, dysplasia of the vulvar skin as determined by colposcopy and a Lichen-score < 5. During the length of the study the participants were not allowed to use topical or systemic corticosteroids.

All participants gave oral and written informed consent.

For anaesthetics, we used topical lidocaine cream 30% that was applied 20 min prior to laser therapy. The patient was given the cream to be applied by the patient herself including some medical gauze to be put on top of it and to allow the cream to settle properly whilst the patient was sitting down in the waiting area. Before laser therapy, the cream was thoroughly removed to ensure appropriate laser effect.

We used a microablative fractional CO_2 Lasersystem (SmartXide Touch C60, MonaLisa Touch, DEKA, Florence, Italy). For the vulvar use the Hi-Scan V^2LR scanning system was connected.

Immediately before laser application all patients received lidocaine cream 30% locally that was applied on the vulva region and was removed after 10 min.

Laser application was performed in the semi upright position on a gynaecological examination chair.

Radiation of the normal dosed group was adjusted with power 24 W, exposure time 400 microsec, DOT spacing 1000. Low dose group received a lower dose of power 0, 5 W, exposure time and DOT spacing remain the same.

Except for the different radiation dose patients underwent exactly the same regimen concerning application time, local anaesthetic and post treatment advices.

All participants underwent totally five consultations. During the first consultation (T0) we screened the inclusion and exclusion criteria, gave all information about the study and the participants signed informed consent. We performed a vulvar examination, photo documentation of the vulva and additionally urine pregnancy test in all premenopausal women.

At the second consultation (T1), after randomization, we determined the lichen score and started the first treatment with a laser dose depending on randomization.

The lichen score consists of a validated scoring system evaluating erosions and hyperkeratosis, fissures, agglutination, stenosis and atrophy using 0 to 2 points per domain. A score of >4 determines the likelihood of lichen sclerosis in >90% [4].

The participants completed two validated questionnaires: visual analogue scale (VAS) of current symptoms, FSFI-female sexual function index). For sexual function, we used the Female Sexual function Index (FSFI) questionnaire. The FSFI is a questionnaire consisting of 19 questions, which refer to the domains desire, arousal, lubrication, orgasm, and satisfaction. For each question, there is a score range from 0–5 and 1–5 respectively as described in the FSFI scoring appendix [14].

VAS asked the patients for the main disturbance by lichen including itching, burning and discomfort. The exact wording was "How much are you disturbed by your symptoms of lichen? Please rate your symptom bother between 0 = no disturbance to 10 = most imaginable disturbance."

At all consecutive meetings (T2-4) we performed a vulvar examination and photo documentation. Three subsequent treatments of laser application followed in time intervals of three weeks, at all meetings the women completed a VAS of their actual symptoms and answered the FSFI questionnaire. At the fourth and fifth meeting (T3 and T4) the lichen score was performed.

Overall quality of life concerning lichen was assessed by asking the patients with the exact wording "How has your quality of life concerning lichen developed since last time?" with the options 1. Better; 2. Same or 3. Worse than during the last visit.

The sample size is based on the primary outcome, the changes from baseline to six weeks after tretamtent (i.e. three months after baseline) on a VAS rating symptoms on a range from 0 to 10.

We regarded a difference in the change of VAS of 2 as clinically significant. The standard deviation is derived from a publication by Bizjak Ogrinc et al [15–16]. They reported a change on a summary VAS ranging from 0 to 30 of 17.5 (95% confidence interval 14.4–20.5) at three months in 20 patients receiving non-ablative laser therapy. In the control group of 16 patients, the change was 9.1 (95% CI 5.0–13.2).

We calculated the standard deviation from these confidence intervals and scaled it to range from 0 to 10. This resulted in a standard deviation of 2.3 and 2.8 for the laser and the control group, respectively. Based on these assumptions, a power of 80% and a two-sided aplpha lever of 0.05, a two sample means test yields a total sample size of 58 patients. To account for dropouts of up to 10%, we enlarged the sample size to 64 patients (32 in each group, GraphPad©version 9.0 for Windows).

Results

The Consort diagram describes the progress through the phases if the

trial as follows:

Table1: Patients' characteristics.

Primary endpoint

Before treatment mean VAS-Score in the normal dose laser group was **4.26 (±2.39 SD)**. In the low dose laser group the VAS Score was **5.14 (±2.56 SD).**

After the first treatment mean VAS-Sore in the normal dose laser group was 3.44 (±1.91 SD). In the low dose laser group the VAS Score was equal **3.65 (±1.89 SD)**, both highly significant (<0.0001).

However, after 18 weeks, the difference between the mean VAS scores in the normal dose laser group and low dose laser group was not significant ($p = 0.6244$).

Secondary endpoints

Lichen score developed as follows.

Before the laser application the mean LS was **7.4 (±1.7)** and after the treatment **4.1 (±2.2).** In the normal dose laser group the first LSc was **7.2 (±1.6)** and in the end **3.9 (±2.1),** the difference is significant ($p < 0.0001$). In the low dose laser group the LS at the beginning was **7.5 (±1.7)** and after treatment **4.3 (±2.4)**, the reduction of the parameters is highly significant ($p < 0.0001$) in both groups.

The mean reduction in the normal dose laser group for the LS was **3.4** and for the low dose laser group **3.3**. The difference between the two groups is not significant ($p = 0.88$).

Sexual activity

Thirty-one of the women reported to be sexual active.

In the low dose laser group 13 patients (45%) were sexually active before the treatment, 11 (38%) patients were not sexually active because of lichen sclerosus, 5 (17%) patients were sexually not active for other reasons (no partner, partner with health issues etc.).

After the treatment 16 (55%) patients were sexually active, only 7 (24%) were not sexually active because of lichen sclerosus, 6 (21%) for other reasons.

In the normal dose laser group were 18 (53%) patients sexually active before the treatment, 10 (29%) patients were not sexually active due to the lichen sclerosus, 6 (18%) patients were sexually not active due to other reasons.

After the treatment 23 (67%) patients were sexually active, only five (15%) were not sexually active due to lichen sclerosus, six (18%) due to other reasons.

The improvement in sexual activity was not significant different in both groups ($p = 0.61$).

FSFI questionnaires were incompletely filled in and full of gaps of about 55%, and due to this finding we were unfortunately not able to determine sexual function in detail.

Quality of life

At the beginning of our study four women reported to have no limitations or restrictio The exact wording was "Do you feel restricted in your every day activities?" with possible answers yes, no or unsure.ns in everyday life, one of them of the LDG, three of the NDG.

In the low dose laser group, 15 (52%) patients reported severe limitations and 13 (45%) indicated intermittent restrictions before the laser application started. After the laser treatment one (3%) patient had no more restrictions, seven (20%) patients reported severe and 20 (77%) intermittent restrictions. We were able to detect an improvement in eight patients (53%).

In the normal dose laser group before the treatment 17 (50%) patients described severe and 14 (41%) intermittent limitations. After the treatment seven (23%) patients reported severe and 24 (77%) intermittent restrictions. We could detect an improvement in ten participants (58%).

In the normal dose laser group 14 (41%) patients had an improvement in the QoL in the low dose laser group eleven patients (38%) had an improvement, this difference was not significant ($p = 0.80$).

Table 1
Summarizes patients' baseline characteristics.

Laser group	Mean age (years; range)	Mean weight (kg, range)	Menopause status (1 = premenopausal, 2 = postmenopausal)
Normal dose laser (n = 34)	52 (20–79)	67.5 (55–81.5)	1: n = 12 2: n = 22
Low dose laser (n = 29)	53 (21–80)	66.2 (54–80.5)	1: n = 13 2: n = 16

Side effects

Thirty-one experienced some burning sensation during the laser application not requiring intervention. This burning sensation lasted up to 12 h and the disappeared.

No significant discomfort or side effects were reported, neither during laser treatment nor immediately after or at the follow-up visit.

Discussion

The current prospective randomized study shows an improvement of symptoms and lichen score in patients with lichen sclerosus in the absence of serious short term or long- term side effects. Surprisingly, the normal dose laser group and the low dose laser group – that was initially meant to work as placebo!- showed these improvements. To note, no activation of lichen was detected (Koebner phenomenon), which is reassuring for future lichen patients who desire to undergo laser treatment.

One of the strength of our study is the large and adaequately powered number of patients, with a constant participation, few drop-outs and a small number of exclusions. We noticed during the time of the repeated applications a clear satisfaction of most participants. Maybe the frequent medical contact with the patients and the intensive discussion about their subjective feelings concerning their symptoms provokes some kind of a placebo effect. We know that this dermatosis causes intermittent uncertainty in process and prognosis and an advisory is essential.

Weakness of this study was the poorly filled in FSFI questionnaire that finally was insufficient to draw any conclusion. An explanation for this may be the embarrassment of the patients when it comes to sexual function. We will take this into consideration for future studies.

Rather surprisingly, we detected some effect of our "placebo" group, meaning a low dose laser application that we initially considered as sham application. In conclusion, we may say that even low energy density can nevertheless lead to an improvement of LS.

Meanwhile many studies are published [12,15–18] that confirm that the fractional CO2-Laser as considered alternative to corticosteroids during therapy in LS.

However, there is still a lack of evidence to recommend laser application for the treatment of genital LS. A systematic review [16] pointed out many limitations of previous studies, e.g. no peer review, no prospectively published study protocol. Many studies are under-powered. Published case series lacked methodological details and confounding factors, including concomitant use of topical treatments such as potent or ultra-potent topical corticosteroids or estrogen. Some of the studies are either commercially funded or declare conflicts of interest. In some studies it is not apparent how LS was diagnosed. Laser application was compared with either topical corticosteroid, sham laser or ultrasound treatment.

Various studies used different types of laser (diode laser, non-

ablative neodymium: yttrium aluminium garnet (Nd:YAG) laser and fractional CO2 laser with varying regimens.

We know that a thermal reaction of the tissue is one of the effects we used for a therapeutic effect in medical use of the laser. Molecules are activated which trigger chemical reaction in the cells. Initial inflammatory response as indicated by statistically significant induction of proinflammatory cytokines (interleukin-1β and tumour necrosis factor-α). This was followed by substantial increases in levels of several matrix metalloproteinases and later by significant induction of type I collagen. Dermal remodelling was noted [19].

We used the fractional ablative CO2-Laser comparing two different dosages of power. In application of different power (wattage) we expect different photochemical effects. However, we were not able to prove a significant difference in both groups, neither in subjective appraisal, nor in objective parameters. We can postulate that this therapy is effective, but we cannot recommend the optimal dosage of power.

Thermic reactions are always associated with charges of the surrounding tissue that depends near to other parameters from the power of application. Another question could be the influence of DOT spacing and/ or exposure time of the therapeutic effect.

Additionally we do not have sufficient information and data about the sustainability of the positive effects of this treatment. Long time follow-up is mandatory.

Laser therapy is an expensive therapy, the cost of the laser device, costs of frequent medical consultation time is in contrast to a medical prescription of a topical treatment with occasional follow-up inspections. Laser therapy is currently not covered by health insurance in Switzerland. However, laser may help to reduce steroid consumption and steroid side effects.

Another possibility for treating LS would be Erbium YAG laser [20]. The results of this study showed that Er:YAG laser treatment significantly reduces symptoms of lichen sclerosus such as itching and vulvar pain, but not coital pain. Improvement after treatment was significant in clinical signs (ecchymosis, excoriations, and hypopigmentation), and some improvement was detected in labial fusion and hyperkeratosis. No improvement was observed in effacement. Laser treatment was well tolerated by patients and significantly reduced the impact of lichen sclerosus on patients' lives.

As for the mechanism of action, metalloproteinases may play a role. Matrix metalloproteinases (MMPs), also known as matrix metallopeptidases or matrixins, are metalloproteinases that are calcium-dependent zinc-containing endopeptidases.

Collectively, these enzymes are capable of degrading all kinds of extracellular matrix proteins, but also can process a number of bioactive molecules. A recent study showed that matrix metalloproteinase 8 levels in the laser group were notably lower than those in the control group 3 months after treatment ($p < 0.001$) [21].

Although the study has been finished are all patients still being followed up in our clinical setting as many questions still remain open:

In which intervals has the laser application to be repeated, and for how long does this positive effect remain?

We did not assess absorbtion of the local anaesthetic cream that was applied before laser therapy; however, this could be an issue for future studies.

Future adaequately powered studies possibly including the combination of local steroids and laser therapy are necessary.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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