
Peer Review File

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Reviewer A

1) First, the correct clinical research design should be a retrospective comparative cohort study.

Re: I modified it as follows:

2
3 | [A retrospective comparative cohort study of ultra-pulse CO₂ lattice laser and](#)
4 | [glucocorticoids in the treatment of vulvar epithelial nonneoplastic lesions](#)
5
6 | Dongmei Wei¹, Jijie Li², Yueting Zhang¹, Jian Meng¹, Yueyue Chen¹, Xiaoyu Niu¹
7

2) Second, the abstract needs some revisions. The background did not indicate the knowledge gaps on the influence of pathological type on the treatment efficacy and the relative efficacy of CO₂ lattice laser vs. glucocorticoids. The methods did not describe the inclusion of subjects, how the two treatments were assigned, duration of intervention, and measurements of efficacy and safety outcomes. The results need to first report the number of subjects who completed the intervention and follow up. The authors need to quantify the findings by reporting effect size measures and accurate P values. The current conclusion needs to be tone down since this is not a RCT.

Re: I modified it as follows:

31 | Methods: [From November 2016 to July 2018, 178 cases of vulvar LSC or lichen](#)
32 | [simplex chronicus were confirmed with vulvar biopsy at our institute. Finally, 160](#)
33 | [patients were enrolled in this trial. After matching according to age, pathological](#)
34 | [subtype, and severity of the disease, the patients were divided into 2 groups: a group](#)

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35 | [treated with topical hormone and a group treated with CO₂ lattice laser therapies.](#)
36 | [There were 80 cases in each group, including 40 with LSC and 40 with lichen simplex](#)
37 | [chronicus. Each group contained 40 samples of lichen simplex chronicus \(LSC\) and](#)
38 | [40 samples of lichen simplex chronicus treated with CO₂ lattice laser and](#)
39 | [glucocorticoids, respectively. With the CO₂ laser multifunctional platform, each](#)
40 | [person received a course of 3 sessions at 4-week intervals. This therapy last 1 week.](#)
41 | [Patients applied 1 gram of progesterone cream and betamethasone cream to the](#)

3) Third, the introduction of the main text needs to have an extensive review on the efficacy and safety of available treatments for nonneoplastic lesions of vulvar epithelium and factors associated with the treatment efficacy. It is also necessary to analyze the clinical needs to compare CO₂ lattice laser vs. glucocorticoids and indicate the knowledge gaps on their relative efficacy.

Re: I modified it as follows:

91 the CO₂ lattice laser have been reported.
92 Vulvar lichen sclerosis (VLS) is a rare chronic inflammatory non-neoplastic skin lesion
93 of the female vulva. The main clinical manifestations are vulvar itching and burning

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95 pain. Abnormal anatomical structure and abnormal shape can lead to dysuria, painful
96 inter-course, and unsatisfactory sex life, which will affect the life of couples and cause
97 great troubles to women's physiology and psychology. At present, VLS is an incurable
98 disease. The main purpose of treatment is to control the subjective and objective
99 symptoms of patients. The main treatment method is local application of
100 glucocorticoids. After 3-4 months of continuous local treatment of glucocorticoids,
101 more than 50% of the patients' clinical symptoms disappear and lesions such as
102 hyperkeratosis, bleeding and chafing are significantly improved. It should be
103 emphasized that as the frequency of dosing decreases and patients experience
104 recurrence of symptoms or signs, the frequency of dosing needs to be readjusted and
105 increased, and therefore patient compliance with dosing decreases. A series of adverse
106 reactions, such as skin atrophy, pigmentation, telangiectasia, and secondary infection.
107 In recent years, fractional CO₂ laser has been gradually accepted by patients due to its
108 almost non-invasive therapeutic advantages, but its specific therapeutic effect and
109 adverse reactions are still unclear. Some clinical data are urgently needed to confirm its
110 efficacy and adverse reactions, so as to provide patients with better treatment
111 recommendations.

4) Fourth, the methodology of the main text, please describe the clinical research design, sample size estimation, detailed procedures for matching age, pathological subtype, and severity of the disease of the two groups, and measurements of safety outcomes. In statistics, I suggest the authors to use multiple regression analyses to ascertain the relationships between pathological subtype and treatment and the treatment response by adjusting for the confounding effects of clinical covariates. The current study only did univariate analyses, which is not adequate and has confounding bias. Please ensure $P < 0.05$ is two-sided.

Re: Because the total number of cases is small, and there are not many types in each subgroup, GeorgZimmermann1 et al reported that the number of covariance statistics is too small, which will affect the accuracy of the results. We will continue to expand the sample size in follow-up studies to better evaluate the relationship between pathological subtypes and treatment techniques and treatment effects.

1. Georg Zimmermann, Meinhard Kieser & Arne C. Bathke (2020) Sample size calculation and blinded recalculation for analysis of covariance models with multiple random covariates, Journal of Biopharmaceutical Statistics, 30:1, 143-159

Reviewer B

1. Abstract: the background of this study needs to be briefly explained in the objective part.

Reply: I modified it.

Changes in the text:

25 Abstract

26 **Background:** A comparison of topical glucocorticoids with CO₂ fractional laser

27 treatment was conducted to investigate the differences in the efficacy of

28 non-neoplastic vulvar epithelial lesion treatments in different pathological types and

29 to provide a scientific basis for the management of these disorders.

30 **Objective:** To study the difference of curative effect of different pathological types of

31 non-tumor vulvar epithelial lesions and provide scientific basis for the treatment of

32 these diseases.

33 **Methods:** From November 2016 to July 2018, 178 cases of vulvar LSC or Lichen

34 sclerosus, were confirmed with vulvar biopsy at our institute. Finally, 160 patients

2. Statistical details, such as what statistical test, single-tailed test or double-tailed test are used, need to be clearly stated in the text or table legend. What analysis does the P value displayed in each table belong to?

Reply: I modified it, double-tailed test.

Changes in the text:

137 ##Statistical methods

138 SAS 9.3 software (SAS Institute) was used to conduct the statistical analysis. The

139 comparison of the data of normal distribution uses t test or analysis of variance, and

140 the data that does not conform to the normal distribution is described as the median.

141 The case number, constituent ratios, and the disordered classified data were calculated.

142 χ^2 test was used to compare the classified counting data. Double-tailed test are used.

143 $P < 0.05$ indicated a statistically significant difference.

Table 1 The basic characteristics of the patients at baseline

Patients	Laser (N=80)	Glucocorticoids (N=80)	Double-tailed t test	P
Age(years)	44.89±11.52	42.09±10.30	0.41	0.854
BMI(kg/m ²)	23.95±3.03	22.78±3.21	0.65	0.511
Course of disease	3.71±2.46	3.02±2.66	0.49	0.452
Clinical score before treatment	6.63±1.20	6.51±1.61	0.08	0.914

Data is displayed using (mean ± standard deviation). BMI, body mass index.

3. Please indicate whether this study is a double-blind trial, a single-blind trial or an open study.

Reply: I modified it.

Changes in the text:

108 medical problems, (IV) and those participants with mental or spiritual disorders that

109 prevented them from completing follow-up visits. Finally, 160 patients were enrolled

110 in this trial. This study is a double-blind trial. After matching according to age,

111 pathological subtype, and severity of the disease, the patients were divided into 2

4. What is the mechanism of super-pulsed CO2 lattice laser combined with glucocorticoid in the treatment of non-tumor lesions of vulva epithelium?

Reply: I modified it.

Changes in the text:

247 therapeutic responses, and the reasons for this need to be further investigated. The
 248 mechanism of combined treatment of the two may be: the thermal, photochemical,
 249 and pressure effects of hormone combined with CO2 can stimulate the healing of
 250 newly formed squamous epithelial wounds by resecting local vulvar lesions.
 251 Combined treatment of the two can enhance the expression of VEGF in tissues in a
 252 short period of time, effectively improve the microvascular status of local vulvar
 253 lesions, promote tissue angiogenesis and repair of damaged tissues, and increase the
 254 number of microvessels in the dermis. Thereby improving the state of local ischemia
 255 and hypoxia, and promoting the rehabilitation of diseased skin; At the same time,

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256 combined treatment of both can reverse the disorder of cell cycle in vulvar lesions,
 257 thereby improving the condition of vulvar lesions.

Reviewer C

1. Reporting Checklist

Please double check ALL items in the checklist, you filled the same paragraph in different items. For example, “Methods/Paragraph 5-9” was filled in items 3-11, the first line of item 3 was not shown in the Methods/Paragraph 5-9 but in Methods/Paragraph 1, please check the whole checklist and revise.

Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	Page 3-4/Line 59-92	Methods/Paragraph 5-9
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	Page 3-4/Line 59-92	Methods/Paragraph 5-9
		• Recruitment setting	Page 3-4/Line 59-92	Methods/Paragraph 5-9
		• Settings and locations where the data were collected	Page 3-4/Line 59-92	Methods/Paragraph 5-9
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	Page 3-4/Line 59-92	Methods/Paragraph 5-9
		o Content: what was given?	Page 3-4/Line 59-92	Methods/Paragraph 5-9
		o Delivery method: how was the content given?	Page 3-4/Line 59-92	Methods/Paragraph 5-9
		o Unit of delivery: how were the subjects grouped during delivery?	Page 3-4/Line 59-92	Methods/Paragraph 5-9
		o Deliverer: who delivered the intervention?	Page 3-4/Line 59-92	Methods/Paragraph 5-9
		o Setting: where was the intervention delivered?	Page 3-4/Line 59-92	Methods/Paragraph 5-9
		o Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	Page 3-4/Line 59-92	Methods/Paragraph 5-9

Reply 3: I check ALL items in the checklist.

2. Table 1

a) Please provide the unit for age and BMI.

Reply: I provided the unit for age and BMI.

b) Please add the description to the table footnote that how the data are presented in table.

Reply: Data is displayed using (mean ± standard deviation)

c) Please defined BMI in the table footnote.

Reply: BMI: body mass index

Changes in the text:

381 | Table 1 The basic characteristics of the patients at baseline

Patients	Laser (N=80)	Glucocorticoids (N=80)	Statistical value	P
Age(years)	44.89±11.52	42.09±10.30	0.41	0.854
BMI(kg/m ²)	23.95±3.03	22.78±3.21	0.65	0.511
Course of disease	3.71±2.46	3.02±2.66	0.49	0.452
Clinical score before treatment	6.63±1.20	6.51±1.61	0.08	0.914

382 | Note: Data is displayed using (mean ± standard deviation);BMI: body mass index

383 |

3. Table 3

Please add the description to the table footnote that what data are presented in table.

score	treatment	treatment	treatment
Laser (N=80)	2.5±2.2	2.1±2.0	2.1±2.0
Glucocorticoids (N=80)	3.8±2.8	4.5±3.5	5.5±3.8

Reply: changes in the text:

Table 3 Efficacy scoring pretreatment and at 1-, 3-, and 6-month posttreatment

Curative effect score	One-month treatment	Three-month treatment	Six-month treatment
Laser (N=80)	2.5±2.2	2.1±2.0	2.1±2.0
Glucocorticoids (N=80)	3.8±2.8	4.5±3.5	5.5±3.8

Note: Data is displayed using (mean ± standard deviation)

4. References/Citations

a) Please check if the author's name matches with the citation.

261 months of treatment. This finding is similar to that of Peterson et al. (11), who reported
262 that patients with vulvar lichen simplex chronicus treated with CO₂ laser had a normal

Reply: I check the author's name.

Changes in the text:

216 nonneoplastic lesions of the vulvar epithelium and repairs damaged tissue from local
217 scratching (1). In our study, the efficacy of CO₂ lattice laser and glucocorticoids was
218 more than 50% at 1, 3, and 6 months of treatment. This finding is similar to that of
219 Mautz TT et al. (11), who reported that patients with vulvar lichen simplex chronicus
220 treated with CO₂ laser had a normal regenerating epithelium of the vulvar tissue and
221 prolonged duration of symptoms (2–3 years).

b) In the reference list, there's no Peterson's study, please add the study to the reference list and add the citation in the sentence.

286 treatment group experiencing the most pronounced effect. This result is consistent with
287 that of Peterson et al., who reported that twenty-three adult women received CO₂ laser
288 treatment, which significantly improved the scores of all scales from baseline to T4
289 questionnaire. CO₂ laser has been proved to be effective for VLS symptoms and can

Reply: I check the reference.

Changes in the text:

239 laser treatment group experiencing the most pronounced effect. This result is
240 consistent with that of Mautz TT et al., who reported that twenty-three adult women
241 received CO₂ laser treatment, which significantly improved the scores of all scales
242 from baseline to T4 questionnaire. CO₂ laser has been proved to be effective for VLS
243 symptoms and can be regarded as a substitute for corticosteroids during maintenance