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## Review Article

# Oral Lichen Planus Treatment by CO<sub>2</sub> Laser: A Systematic Review

<sup>1</sup>Hamid Reza Mozaffari, <sup>2</sup>Narges Ziaei, <sup>3</sup>Hesameddin Nazari, <sup>4</sup>Seyed Mojtaba Amiri and <sup>5</sup>Roohollah Sharifi

<sup>1</sup>Department of Oral Medicine, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>2</sup>Department of Periodontics, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>3</sup>Department of Oromaxillofacial Surgery, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>4</sup>Department of Biostatistics and Epidemiology, School of Health, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>5</sup>Department of Endodontics, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran

## Abstract

The laser has recently been used as a new treatment method for removal of Oral Lichen Planus (OLP) symptoms and signs. The current study was aimed to evaluate the impact of CO<sub>2</sub> laser therapy on OLP lesions. All the details of this study were designed and implemented according to the preferred reporting items for PRISMA. Seven databases were used for searching the articles, including MEDLINE/PubMed, Web of Knowledge, Cochrane Central Register of Controlled Trials (CENTRAL), Science Direct, Scopus, EBSCO and DOAJ. Only the articles written in English were included in the study. Seven out of 476 papers were eligible for systematic review according to the determined parameters. Intragroup analyses of CO<sub>2</sub> laser indicated that the lesion size and pain level were reduced significantly after laser therapy. Further, the findings of studies with drug comparison groups showed that laser exerted a significantly greater impact than drug. The effects of CO<sub>2</sub> laser on OLP were reported to be significant in both short-term and long-term follow-ups compared with other control groups. However, further studies are required to be conducted with standards of randomized controlled clinical trials and standardized measurement of results with reliable severity scoring tools.

**Key words:** Oral lichen planus, CO<sub>2</sub> laser, systematic review, pain, laser therapy, visual analog scale, drug, postoperative care, clinical trial, case series

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**Corresponding Author:** Roohollah Sharifi, Department of Endodontics, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran

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**Competing Interest:** The authors have declared that no competing interest exists.

**Data Availability:** All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Oral Lichen Planus (OLP) is a chronic cutaneous disease involving the oral mucosa<sup>1</sup> with a mean age of onset in the 4th and 5th decade that has more prevalence in females<sup>2</sup>. The etiology of OLP is unknown<sup>3</sup> and its prevalence has been reported to be 0.5-2.2% in various studies<sup>4-9</sup>. There is an evidence to support the role of immune system in the development of this disease<sup>10</sup>. This has been confirmed by histopathological characteristics such as the presence of a band-formed infiltrate dominated by T-lymphocytes under the epithelium. The OLP can clinically be seen as white and red components. Based on its white and red components, OLP can be generally classified into six categories: Reticular, papular, erythematous, bullous, plaque-like and ulcerative<sup>6</sup>. Burning sensation is the most common complaint of patients with this disease. The OLP is also proposed as a premalignant lesion. However, the risk of its transformation to malignancy is highly controversial<sup>11</sup>. Therefore, the most important complication of OLP is the development of oral squamous cell carcinoma (OSCC)<sup>12</sup> that represents about 90% of all oral malignancies<sup>13</sup>. So far, any definite treatment has not been proposed for OLP. All therapeutic strategies used for OLP are based on the reduction or elimination of the symptoms of disease, which are mainly conservative and are carried out with topical and systemic medications. Topical corticosteroids are used as the first line treatment for OLP, but they cause complications like thinning of oral mucosa, secondary Candida infection, tachyphylaxis and adrenal suppression<sup>14</sup>. The laser has recently been used as a new treatment method for removal of OLP symptoms and signs. The biological effects of laser on small nerve fibers are due to cytoplasmic changes of adenosine 3', 5'-cyclic monophosphate (cAMP), Ca<sup>++</sup>, pH, increased blood circulation and improved lymphatic drainage and increased plasma concentration of prostaglandin, endorphin and enkephalin<sup>15-17</sup>. The CO<sub>2</sub> laser has been found to be effective due to absorption of water during ablation of oral mucosa soft tissue lesions, including leukoplakia and OLP<sup>15,18-20</sup>. Herein, we evaluated the impact of CO<sub>2</sub> laser therapy on OLP lesions in a systematic review study.

## ELIGIBILITY CRITERIA

This study was approved by the Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran. All the details of this study were designed and performed according to the preferred reporting items for systematic

reviews and meta-analyses (PRISMA)<sup>21</sup>. Only the articles written in English were considered in the study. The papers with all required criteria were submitted to data extraction. The eligibility criteria have presented below:

- **Type of study:** Randomized-controlled clinical trials, controlled clinical trials, prospective clinical studies, retrospective clinical studies and case series
- **Type of intervention:** CO<sub>2</sub> laser with all powers, device specifications, prescription style and treatment duration
- **Patient:** OLP patients
- **Follow-up period:** ≥3 month
- **Type of outcome measurement:** The most outcomes were evaluated clinically, including improvement in clinical signs and symptoms reported by the patient

## SEARCH STRATEGY

Seven databases were used for searching the articles until January 25, 2016 for eligible studies, including MEDLINE/PubMed, Web of Knowledge, Cochrane Central Register of Controlled Trials (CENTRAL), Science Direct, Scopus, EBSCO and DOAJ. The Oral Lichen Planus combined with Laser was searched in database of PubMed and also in other databases.

## OUTCOMES

The primary outcomes were pain reduction by visual analog scale (VAS)<sup>22</sup> reported by the patient, physician's overall assessment of signs and patient's self-assessment, whereas, secondary outcomes were reduced size of lesion, transformation of lesion to malignancy and reported complications of treatment.

## ASSESSMENT OF HETEROGENEITY

Heterogeneity of output variables in all studies was detected by the following factors:

- Study design
- Evaluation period
- Medications after laser therapy
- Lost to follow-up
- Side effects
- Industry (commercial) funding

### QUALITY ASSESSMENT

The NZ and SMA searched the studies based on criteria. Then, two reviewers (HRM and HN) screened all titles and abstracts of the eligible papers based on the eligibility aspects. The reviewers evaluated the methodological quality of the selected studies by the proposed checklist of Cochrane reviewer's handbook<sup>23</sup> for randomized clinical trials: Sequence generation, allocation concealment, personnel and outcome assessors, blinding of participants, incomplete outcome data, selective outcome reporting and other sources of bias. The MINORS checklist<sup>24</sup> was used for non-randomized clinical trials. The disagreements between the reviewers were discussed. If the discussion continued, the final decision was made by third reviewer (RS). In this checklist, the score of 20 was selected for inclusion in the systematic review. Also, the checklist by Moga *et al.*<sup>25</sup> was used for case series that the suggested the score 15 was chosen for inclusion in the systematic review.

### STATISTICAL ANALYSES

Data were extracted from the papers with required criteria for the subsequent analysis. They were included study design, follow-up period, number of patients, study groups, postoperative care, results of each group and comparison between groups. The obtained data from the papers indicated

a clear heterogeneity in different aspects of analysis, so meta-analysis was impossible to be conducted. Hence, they were summarized and reported descriptively.

### RESULTS OF SEARCHING AND SELECTION

A total of 417 papers was obtained through searches (Fig. 1). After screening the titles and abstracts, 12 papers were selected and the others were excluded. Reading the full text of papers, five papers were excluded from the study due to performing laser intervention on different oral lesions that OLP was only a small part of these lesions. Reviewing the list of references, no other relevant study was detected. Thus, seven papers were eligible for the systematic review according to the determined parameters<sup>11,17,26-30</sup>. Two out of seven papers were case series<sup>17,28</sup>, one retrospective cohort study<sup>11</sup> and four articles were clinical trials with comparison groups<sup>26,27,29,30</sup>. From these four papers, two of them evaluated the short-term effects<sup>26,30</sup> and two studies assessed the long-term effects of CO<sub>2</sub> laser on OLP<sup>27,29</sup>.

### ASSESSMENT OF HETEROGENEITY

Heterogeneity was observed in some studies included in the systematic review, including study design, laser type, follow-up period and study outcome. The details are presented in Table 1.

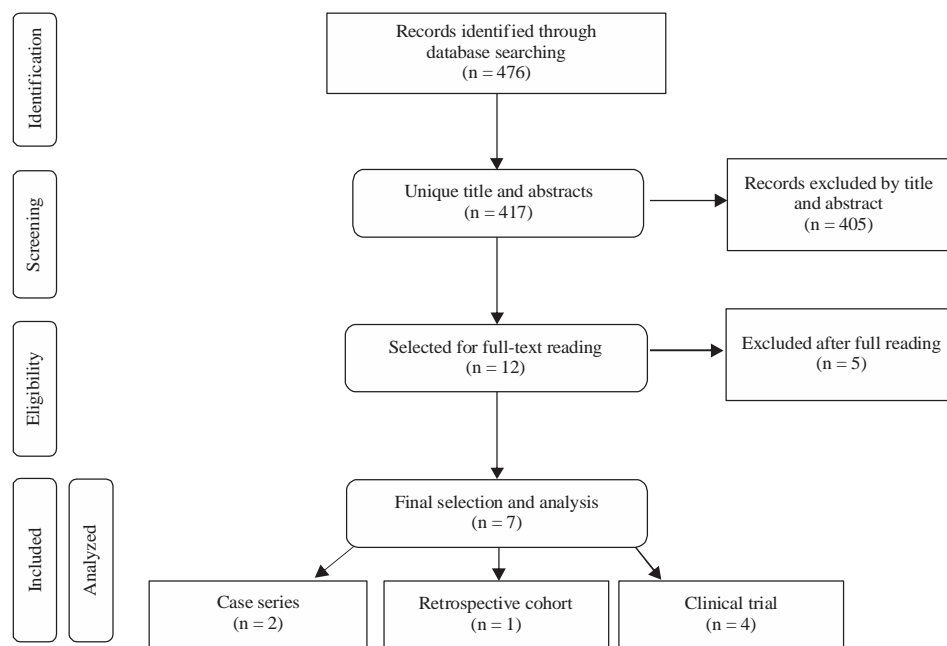


Fig. 1: Search, selection and analysis processes

Table 1: Overview of the studies processed for data extraction

References	Title	Study design and follow-up time	No. of participants baseline (end), gender, age (mean/range), characteristics	Groups	Postoperative care	Conclusions of the authors of the original papers
Vander Hem <i>et al.</i> <sup>11</sup>	CO <sub>2</sub> laser evaporation of OLP	Retrospective study (18 years)	21-(21) ♀ 0.7:1 ♂ Mean age: 52.3 Range: 34-62	CO <sub>2</sub> laser	0.1% chlorhexidine mouthwash and paracetamol analgesic	CO <sub>2</sub> laser evaporation was a good treatment option for OLP and could even be considered as first choice.
Pakfetrat <i>et al.</i> <sup>17</sup>	Removal of refractory erosive-atrophic lichen planus by the CO <sub>2</sub> laser	Case series (3 months)	10-(10) ♀:7, ♂:3 Mean age: 49.6 Range: 35-64	CO <sub>2</sub> laser at continuous-wave mode with power of 5 W (Daeshin, model DS-40U, Daeshin Enterprise Corp, Guro-gu, Seoul, Korea)	A persica mouthwash (containing an extract of <i>Salvadora persica</i> ) and a NSAID were prescribed for postoperative care	The results indicated that the CO <sub>2</sub> laser surgery was an effective modality for management of erosive-atrophic OLP and could be considered as a suitable alternative to standard treatment
Agha-Hosseini <i>et al.</i> <sup>26</sup>	Comparative evaluation of low-level laser and CO <sub>2</sub> laser in treatment of patients with OLP	RCT (3 months)	28-(28) ♀:21, ♂:7 Mean age: 50.7 Range: 21-69	a: CO <sub>2</sub> 10,600 nm, 3 W (Deka, Italy) b: LLLT using a diode laser (Mustang, Russia) with two probes, infrared light (Ga-As, 890 nm, 0.3-0.5 J cm <sup>-2</sup> ) and red light (633 nm, CW, 0.3-0.5 J cm <sup>-2</sup> )	Diphenhydramin syrup and an analgesic such as a NSAID were prescribed for 2 weeks	In conclusion, this study showed that LLLT displayed better results than CO <sub>2</sub> laser therapy as alternative or additional therapy
Deppe <i>et al.</i> <sup>27</sup>	Different CO <sub>2</sub> laser vaporization protocols for the therapy of oral precancerous lesions and precancerous conditions: A 10-year follow-up	Prospective clinical study (10 years)	145-(119) ♀:?, ♂:? Mean age: ? Range: ?	a: Defocused continuous CO <sub>2</sub> laser beam delivery (continuous wave, 15 W, 5-5 sec, mean output 2.12 W cm <sup>-2</sup> ) b: Continuous-wave mode plus scanner c: Super-pulsed mode plus scanner (pulse duration 80 µsec, pulse energy 20 mJ, mean output 228 W cm <sup>-2</sup> )	Paracetamol, a maximum of one tablet daily (500 mg)	The results of this clinical study indicated that CO <sub>2</sub> laser treatment of premalignant lesions was most efficacious when used in defocused mode
Loh <sup>28</sup>	A clinical investigation of the management of OLP with CO <sub>2</sub> laser surgery	Case series (4 years)	10-(10) ♀:8, ♂:2 Mean age: ? Range: 30-68	CO <sub>2</sub> laser at 20 W machine (Sharplan 1020, Israel)	?	Laser therapy has a sterilization effect and the atraumatic, the noncontact nature of the surgery proved extremely suitable in this regard
Mucke <i>et al.</i> <sup>29</sup>	Clinical trial analyzing the impact of continuous defocused CO <sub>2</sub> laser vaporisation on the malignant transformation of erosive OLP	Prospective clinical study (7 years)	171-(171) ♀:87, ♂:84 Mean age: 52.43 Range: 21-9	a: CO <sub>2</sub> laser by defocused continuous laser beam delivery at 15 W (type 20 C, DEKA, Freising, Germany) b: Local oral saline containing lidocaine hydrochloride (20 mg g <sup>-1</sup> , Dynexan Mundgel, Kreussler Pharma, Wiesbaden, Germany) or systemic diclofenac 50 mg 3 times a day combined with omeprazole 20 mg once a day were administered	?	The CO <sub>2</sub> laser was more effective than local corticosteroid for the treatment
Mozafari <i>et al.</i> <sup>30</sup>	A study of the effects of CO <sub>2</sub> laser therapy on OLP	Clinical trial (6 months)	50-(50) ♀:34, ♂:16 Mean age: 50.22 Range: 27-92	a: CO <sub>2</sub> laser radiation, wavelength of 10600 nm and with maximum power of once 2 W (Spectra Dental Korea 2007) b: Local corticosteroid	Hydrochloride benzydamine mouthwash for 5 days	Radiation of CO <sub>2</sub> laser on OLP lesions that were resistant to local corticosteroid could reduce pain level and lesion size more than therapy with corticosteroid

NSAID: Nonsteroidal anti-inflammatory drug, LLLT: Low-level laser therapy, OLP: Oral lichen planus, RCT: Randomized clinical trial, ? : Unknown/not given

## **STUDY DESIGN, EVALUATION PERIOD AND RESEARCH GROUPS**

All included clinical trials had comparison groups with parallel design. Only one study had used simple random sampling<sup>26</sup>. The follow-up period varied from 3 months to 10 years. Malignancy was reported to be the outcome of two studies<sup>27,29</sup>. Three studies were found to have analyzed pain level<sup>17,11,30</sup>, three studies lesion size<sup>17,26,30</sup> and three studies recurrence rate<sup>27,29,11</sup>.

## **SUBJECT CHARACTERISTICS**

The OLP was recognized according to the clinical and histopathological view. In the most studies, patients were treated with local or systemic corticosteroids before laser therapy, yielding no acceptable result<sup>17,26,11,30</sup>.

## **DRUGS USED AFTER LASER THERAPY**

Some studies used analgesics<sup>17,26,27</sup> and some others used mouthwash<sup>17,11,30</sup>.

## **COMPARISON GROUPS**

In four studies with comparison groups, two studies used drug (local betamethasone, topical lidocaine hydrochloride, diclofenac and systemic omeprazole)<sup>29,30</sup> and two other studies used different types of laser as comparison groups<sup>26,27</sup>. The checklist of Moga *et al.*<sup>25</sup> was used for to evaluate the quality of case series. The study of Loh<sup>28</sup> could not obtain the required score for the systematic review. The quality assessment of non-randomized clinical trials were performed with a MINORS checklist in three studies and they obtained the minimum score specified for inclusion in the systematic review<sup>27,29,30</sup>. The study of Agha-Hosseini *et al.*<sup>26</sup> which was analyzed by the cochrane quality assessment tool, had a high risk of bias. Nevertheless, following a discussion by the authors and given the scarcity of studies in this regard, this research was also included in the systematic review.

## **STUDY OUTCOME**

Intragroup analyses were performed in three studies<sup>17,26,30</sup> and carried out in studies with comparison groups. Table 1 shows the results of data extraction. The data related to changes in each study group and comparison with other groups were determined separately and a summary of results

is presented in Table 2. Meta-analysis was not used due to heterogeneity in study design, laser type, follow-up period and outcome. Intragroup analyses of CO<sub>2</sub> laser indicated that the lesion size and pain level were reduced significantly after laser therapy<sup>17,26,30</sup>. Further, the findings of studies with drug comparison groups showed that laser exerted a significantly greater impact than drug<sup>29,30</sup>.

## **SUMMARY OF THIS REVIEW**

Intragroup analysis showed that treatment of OLP with CO<sub>2</sub> laser was effective in terms of symptom, sign and reduced recurrence and incidence of malignancy. This study showed potential limitations of OLP treatment with CO<sub>2</sub> laser and also evaluated the comparison and judgment about the problems of each study.

## **MEASUREMENT METHOD OF THE LESION SIZE AND PATIENT'S PAIN**

The tools of disease severity scoring in the reviewed studies were heterogeneous. The lesion size and patient's pain, two main symptoms of patients were not evaluated equally at the beginning of treatment and follow-up periods of the studies that some studies quantitatively reported them<sup>17,26,30</sup> and some others only subjectively reported the term "healing"<sup>29,11</sup>. Thus, it was not possible to compare these studies statistically.

## **FOLLOW-UP PERIOD**

The follow-up varied from 3 months to 10 years in the reviewed studies. In the studies with short-term follow-up, higher improvement of the lesion was reported<sup>17,26,30</sup>; 85-100% during a 3-6-month period, while an improvement of 33.4-62% was found for the long-term follow-ups. Nevertheless, OLP is a chronic, relapsing and remitting disease that is based on the possible recurrence of OLP on long-term follow-ups. Loh<sup>28</sup> reported that 80% of cases were improved clinically in a 4 years period and 20% experienced recurrence in a new other location than the site treated with laser. However, lesion recurrence after laser therapy is predictable because laser therapy is a symptomatic treatment not an etiologic. An important issue concerning OLP is the recurrence rate and transformation into malignancy, so that SCC is created in the pre-existing site of OLP. It is important that an OLP lesion may occur again in a long-term period, but laser therapy can be done again to remove the lesion. The

Table 2: A descriptive summary of statistical significances between treatment groups

References	Results in Group(s)	Results with comparison
Van der Hem <i>et al.</i> <sup>1*</sup>	<b>CO<sub>2</sub> laser evaporation:</b> Twenty four lesions (62%) showed no pain and recurrence. Fifteen lesions (38%) showed clinical recurrence and six of these caused pain after complete epithelialization. Nine lesions were without pain	?
Pakfetrat <i>et al.</i> <sup>17**</sup>	<b>CO<sub>2</sub> laser:</b> Lesion size at the end of follow-up was significantly declined compared with the beginning of intervention. The VAS at the end of follow-up was significantly reduced in comparison with the beginning of intervention. Sign score at the end of follow-up was significantly reduced compared to the beginning of intervention	?
Agha-Hosseini <i>et al.</i> <sup>26**</sup>	<b>CO<sub>2</sub> laser:</b> Lesion size at the end of follow-up was lower than the beginning of intervention. The clinical response (sign) at the end of follow-up was significantly improved compared to the beginning of intervention. Symptomatic response at the end of follow-up was improved in comparison with beginning of intervention	Lesion size in LLLT was significantly lower than CO <sub>2</sub> laser. The clinical response (sign) in LLLT group was more significantly improved than CO <sub>2</sub> laser. Symptomatic response in LLLT group was more improved than CO <sub>2</sub> laser
Deppe <i>et al.</i> <sup>27*</sup>	<b>LLLT:</b> Lesion size at the end of follow-up was lower than the beginning of intervention. The clinical response (sign) at the end of follow-up was significantly improved compared to the beginning of intervention. Symptomatic response at the end of follow-up was improved in comparison with beginning of intervention <b>Defocused continuous laser:</b> Five OLPs (41.7%) were successfully treated. One lesion showed malignant transformation to oral SCC	No statistically significant differences were found between groups 2 and 1 and between groups 3 and 1 The symptomatic analgesic treatment of erosive OLP had a significantly higher risk associated with the occurrence of SCC (p<0.0001, OR = 46.33, 95% CI 7.44-288.513) compared with the patients who underwent continuous defocused CO <sub>2</sub> laser treatments
Mucke <i>et al.</i> <sup>29*</sup>	<b>Continuous-wave mode plus scanner:</b> Three oral lichen (33.4%) were successfully treated <b>Super-pulsed mode plus scanner:</b> Four OLPs (50%) were successfully treated	The VAS in CO <sub>2</sub> laser group was significantly lower than drug group. Lesion size at the end of follow-up was significantly lower in CO <sub>2</sub> laser group than in drug group. The EI in CO <sub>2</sub> laser group was significantly higher than drug group
Mozafari <i>et al.</i> <sup>29**</sup>	<b>Defocused CO<sub>2</sub> laser:</b> Twenty six patients (38.2%) developed recurrence of the symptomatic erosive lesions. A total of 42 patients (61.8%) did not have erosive lesions in the follow-up. Two patients (2.9%) developed oral SCC <b>Lidocaine hydrochloride:</b> Ninety patients still showed active lesions of erosive OLP (87.4%), whereas 13 patients (12.6%) had no further erosive OLP in the follow-up period but showed reticular lesions within the oral cavity, 14 patients (13.6%) developed oral SCC <b>CO<sub>2</sub> laser radiation:</b> The VAS was significantly reduced at the end of follow-up compared to the onset of intervention. The lesion size was also significantly reduced at the end of follow-up in comparison with the beginning of intervention <b>Local corticosteroid:</b> The VAS was significantly reduced at the end of follow-up compared to the onset of intervention. The lesion size was also significantly reduced at the end of follow-up in comparison with the beginning of intervention	

\*Long-term follow-up, \*\*Short-term follow-up, VAS: Visual analog scale (scored pain as no pain if pain was 0, mild if pain was 1-4, moderate if pain was 5-7 and severe if pain was 8-10)<sup>27</sup>, LLLT: Low-level laser therapy, CI: Confidence interval, SCC: Squamous cell carcinoma, OLP: Oral lichen planus, OR: Odds ratio, EI: Efficiency index<sup>30</sup>, ?: Unknown/not given

symptomatic analgesic treatment of erosive OLP had a significantly higher risk associated with the occurrence of SCC compared with the patient who underwent continuous defocused CO<sub>2</sub> laser treatment<sup>29</sup>. Planned annual follow-up in these studies seems necessary<sup>29,11</sup>. Some studies used the term Cumulative Disease Free Survival (CDFS) to prevent confusion with disease recurrence<sup>31</sup>. In a study, the chance of transformation to malignancy in OLP cases treated with CO<sub>2</sub> laser was reduced 46 times greater than those with conventional drug treatment<sup>29</sup>. Since the transformation of erosive and atrophic forms to malignancy is more prevalent than other types of OLP<sup>32</sup>, transforming the erosive and atrophic types to reticular one by CO<sub>2</sub> laser would reduce the malignancy rate. In all these studies, the researcher made judgments about the lesion size and efficiency index, while in a standard study; another evaluator blinded to the location of the lesion should report the improvement. Because of the infrequency of OLP samples<sup>11</sup>, some studies included premalignant lesions and vascular malformations to increase the sample size, which were excluded from this study due to histopathological differences of the lesions as well as heterogeneity<sup>33</sup>.

#### **LASER POWER (W)**

The power of each laser device is indicative of its ability. In general, two factors should be considered while working with laser: (a) Type of laser and its wavelength and (b) Power output (average and maximum power should be calculated for pulsed lasers because the maximum power load is greater than the power output in pulse lasers). A laser with high power reaches the treatment dose in a shorter time of radiation<sup>34</sup>. Watt was a factor that was used differently in the reviewed papers. The use of a 2-20 W CO<sub>2</sub> laser was reported in this study.

#### **NON-RANDOMIZED STUDIES**

Due to ethical consideration in study, it was not possible to carry out these studies as randomized trials because the patient was free to choose a laser therapy or conventional treatment methods. Only one study had used a random selection of two laser therapy methods<sup>26</sup>.

#### **SELECTION OF PATIENTS RESISTANT TO ROUTINE TREATMENT**

Another limitation of these studies was that some of them performed laser therapy after systemic and topical treatments.

In fact, they included drug-resistant patients and only one study divided the patients into two treatment groups from the beginning of diagnosis<sup>29</sup>.

#### **INITIAL SEVERITY AND DURATION OF LESION**

Only in the study of Muck *et al.*<sup>29</sup>, the initial severity and duration of the lesion. This is important because new-onset or untreated lesions are usually improved, easier than the long standing refractory lesions even after the washout period. The results of short-term studies<sup>26,30</sup>, indicated a high percentage of success for OLP treatment with laser (100 and 85%, respectively). However, this percentage was significantly declined in long-term studies<sup>27,29,11</sup>, from 33.4-62%. It seems that laser therapy is effective merely in a medium-term range and recurrence of OLP after the laser is predictable in long-term follow-ups.

#### **PUBLICATION BIAS**

The papers included in this review principally reported the beneficial effects of laser. Hence, publication of studies with positive results and significant differences can be indicative of a publication bias, so that some of these studies have not even reported the side effects of laser therapy and merely reported its short-term advantages. Although a formal test was not administered, publication bias should be taken into account.

#### **LANGUAGE BIAS**

Use of only English language studies was another limitation of the present research.

#### **CONCLUSION**

The effects of CO<sub>2</sub> laser on OLP were reported to be significant in both short-term and long-term follow-ups compared with other control groups. However, further studies are required to be conducted with standards of randomized controlled clinical trials and standardized measurement of results with reliable severity scoring tools.

#### **SIGNIFICANT STATEMENTS**

Topical corticosteroids are the first line treatment for OLP and cause a lot of complications, but CO<sub>2</sub> laser has been found to be more effective due to absorption of water during



ablation of oral mucosa soft tissue lesions, including leukoplakia and OLP. Therefore, new developments in laser therapy can reduce complications about the disease and prevent OLP progression compared with the topical treatments.

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