applied sciences

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Review

A Review of CO_2 Laser-Mediated Therapy for Oral Mucosal Lesions

Daniela Condor [1,2], Cristian Culcițchi [2], Rebecca Blum [3], Oana Baru [2,4], Smaranda Buduru [2,5,*], Andreea Kui [5,*] and Ioan Țig [6]

1 Department of Periodontology, "Iuliu Hatieganu" University of Medicine and Pharmacy, 400007 Cluj Napoca, Romania; dr.danacondor@yahoo.com
2 "Stomestet" Dental Clinic, 400372 Cluj Napoca, Romania; cristianculcitchi@gmail.com (C.C.); oanabaru@gmail.com (O.B.)
3 Faculty of Dentistry, "Iuliu Hatieganu" University of Medicine and Pharmacy, 400008 Cluj Napoca, Romania; rebeccablum@umfcluj.ro
4 Experimental Pathology Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, 400008 Cluj Napoca, Romania
5 Department of Prosthetic Dentistry, "Iuliu Hatieganu" University of Medicine and Pharmacy, 400006 Cluj Napoca, Romania
6 Department of Dental Medicine, Faculty of Medicine and Pharmacy, University of Oradea, 410073 Oradea, Romania; nelutig@yahoo.com
* Correspondence: dana.buduru@umfcluj.ro (S.B.); andreeakui@gmail.com (A.K.)

Abstract: (1) Background: Several studies investigating the clinical outcomes of potentially premalignant oral epithelial lesions treated with CO_2 lasers have been published over the last decades. (2) Methods: A systematic research review was performed for studies published between 2011 and 2021 in the PubMed, Science Direct, and Google Scholar databases. (3) Results: Initially, the search identified 52 relevant articles. The primary analysis of the titles and abstracts eliminated 22 articles, leaving 30 articles whose full texts were examined. A total of 22 articles met the inclusion criteria. The studies were classified into 3 categories. (4) Conclusions: After evaluating the results of all the studies included in this review, an initial general statement can be made, namely that CO_2 lasers are a treatment option worth taking into consideration when approaching oral mucosal lesions. When compared to other types of lasers used in dental practice, the CO_2 laser stands out due to its many advantages.

Keywords: CO_2 laser; oral leukoplakia; oral erythroplakia; oral lichen planus; oral dysplasia

Citation: Condor, D.; Culcițchi, C.; Blum, R.; Baru, O.; Buduru, S.; Kui, A.; Țig, I. A Review of CO_2 Laser-Mediated Therapy for Oral Mucosal Lesions. *Appl. Sci.* **2021**, *11*, 7744. https://doi.org/10.3390/app11167744

Academic Editor: Tommaso Lombardi

Received: 14 July 2021
Accepted: 19 August 2021
Published: 23 August 2021

1. Introduction

In 2005, the World Health Organization (WHO) recommended the use of the term "oral potentially malignant disorders" (OPMDs) for any lesion or condition of the oral mucosa that has the potential for malignant transformation. In addition, another term, "potentially premalignant oral epithelial lesions" (PPOELs), has recently been used to describe a number of oral lesions that have malignant potential, such as leukoplakia, erythroplakia, erythroleukoplakia, lichen planus, oral dysplasia, and oral submucous fibrosis (OSF) [1,2].

Leukoplakia commonly appears as white patches and it is considered to be one of the most frequent lesions of the oral cavity. Among other white lesions, leukoplakia is considered to be a premalignant lesion of the oral mucosa, with a variable risk of becoming malignant (between 3 and 30%). The most frequent cancerous development seems to be squamous cell carcinoma (SCC) [3], and early diagnosis of leukoplakia is considered to be of paramount importance.

Oral leukoplakia (OL) might appear in several clinical forms, out of which the most significant are (a) homogeneous leukoplakia, which is the most prevalent type, with a

lower risk of turning into a malignant lesion, and (b) non-homogeneous leukoplakia, which can be identified by thick, hardened, raised surface with red spots, and compared to the homogeneous counterpart, presents a high risk of becoming malignant. Homogeneous leukoplakia usually appears as a white or grey lesion with a uniform aspect and well-defined margins, and it is most frequently located on the jugal, palatal, and lingual mucosa. Non-homogeneous leukoplakia can be subdivided into verrucous, proliferative, nodular, and erythroplakia [3,4].

Oral erythroplakia (OE) has a clinical aspect of a red, velvety plaque or patch that cannot be attributed to any other pathophysiologic process. In some cases, it is associated with oral leukoplakia (erythroleukoplakia). Although the incidence and prevalence of OE are inferior compared to those of OL, the histologic analysis of biopsied homogenous OE lesions showed 51% invasive carcinoma, 40% carcinoma in situ, and 9% mild or moderate dysplasia [1,5].

Oral lichen planus (OLP) is considered a systemic mucocutaneous disease, affecting the oral mucosa, as well as the skin, nails, the scalp, or the vaginal mucosa, with a female predilection [1,6]. Intraorally, the most common sites are the buccal mucosa, gingiva, and tongue, often situated bilaterally and symmetrically, while the most frequent morphologic forms of the disease are the reticular, papular, plaque-like, bullous, atrophic, or erosive forms [7].

Oral submucous fibrosis predominantly affects individuals living in the Southeast Asian countries and, while multiple etiologic factors have been linked to this pathology, it seems that the use of areca nut and its derived products (including betel quid ad gutkha) is the most predominant factor [8,9]. Local symptoms vary from sudden intolerance to spicy foods, associated with the formation of vesicles and ulcers, to xerostomia, restriction of the tongue's range of motion, and a progressive reduction in the elasticity of the oral mucosa [10].

Oral epithelial dysplasia is defined by WHO as a precancerous lesion of stratified squamous epithelium characterized by cellular atypia associated with abnormal maturation and stratification [1,11].

There are several treatment options available in the case of oral leukoplakia, such as drug therapy, surgical excision, freezing, or laser [5,12,13]. The excision of tumorous/pigmented tissue is so far considered to be the best possible solution for obtaining healthy surrounding tissue [3,4]. The classical surgical treatment of tumors is usually considerably invasive, although often a mandatory procedure. As far as malignant lesions are concerned, it is generally acknowledged that their evolution is rapid, may or may not be symptomatic in the initial stages, and that they present unpredictable characteristics of size, appearance, morphology, limits, associated symptoms, and invasiveness in the neighboring tissues [3].

In the case of oral erythroplakia, due to the high risk of malignant transformation, the treatment protocol includes excision to the submucosal level (when the tongue is not involved) or to the superficial muscular level (when the tongue is involved) [1,14,15]. Primary treatment in the case of oral lichen planus includes local medical therapy, such as topical corticosteroids [16], while second-line therapy includes other topical agents (cyclosporine, retinoids, calcineurin inhibitors, etc.) and the use of photodynamic therapy [17].

The treatment protocol for oral submucous fibrosis consists of the removal of risk factors associated with conservative therapy (micronutrient supplementation, antioxidant therapy, enzymatic degradation, and physical rehabilitation) [9,15]. In some cases, surgical therapy is indicated in order to alleviate trismus through excision and the release of fibrotic tissues [8]. Contemporary therapy for oral epithelial dysplasia includes cold knife excision, CO_2 laser ablation, antioxidant therapy, immunomodulating treatment, or any combination of the above [18,19]. However, the risk of recurrence and malignant transformation is high in the case of oral dysplasia [20].

While the excision of tumorous/pigmented tissue is, so far, considered to be the best possible solution for obtaining healthy surrounding tissue [3,4], in the case of laser therapy,

the radiation is absorbed by the water in the tissues and then converted into heat energy, by which the irradiated tissues are removed [21,22]. When using the surgical approach, the aim is to achieve lesion-free margins in the healthy surrounding tissue. However, the consequences of this kind of therapy mainly refer to the loss of soft tissues in the affected area, as well as a complete or partial loss of function and sensitivity in the excised area. The circumferential safety margins that are employed will induce the loss of healthy tissue, the replacement of which is necessary with tissue reconstruction techniques [4]. Depending on the size of the excised area, healing through primary intention may occur when simple suturing techniques can be applied, with or without flap usage. For example, when the lesion excision involves the lingual, sublingual, and/or jugal mucosa, the most frequently used flap is the nasolabial flap [4].

In the case of CO_2 laser, the thermal effect of the laser is used in treating oral leukoplakia lesions. When a CO_2 laser with certain energy irradiates biological tissues, those absorb the laser's energy and transform it to heat energy [23–25]. Under this heat energy, the temperature inside the biological tissue rises rapidly (reaching hundreds of degrees) causing protein coagulation and necrosis [26,27].

Medical professionals around the globe are constantly striving to find therapeutic methods that are as non-invasive as possible while providing more comfort for their patients, during and after the intervention. A laser-based approach appears to be a solution when it comes to the disadvantages of classical surgical therapy. The advantages of laser treatment include shorter operating times, less damage to surrounding tissues, less scarring, less postoperative pain, less swelling and additional intraoperative hemostasis, and surgical precision due to the focused light beam [28–31].

The aim of this review was to investigate the latest outcomes regarding the effectiveness of the CO_2 laser therapy method in the case of potentially premalignant oral epithelial lesions compared with other therapeutic approaches.

2. Materials and Methods

2.1. Search Strategy

A search was conducted in three different databases (PubMed, Science Direct, and Google Scholar), for studies published between 2011 and 2021. The search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P 2015). All eligible articles were also checked for additional references.

2.2. Search Terms

For the search, a combination of the following keywords was used: "carbon dioxide laser", "oral leucoplakia", "oral erythroplakia", "oral lichen planus", "oral tumor laser excision", and"CO_2 laser surgery".

2.3. Article Selection

Two independent reviewers (DC and SB) evaluated the titles and abstracts of the retrieved articles in order to control for selection bias. In situations where it was not clear from the title and abstracts whether an article met the inclusion criteria, the full text was reviewed. If any duplicated reports of the same study were identified, only the most recent was included. Afterwards, full-text articles were evaluated and differences between both reviewers were discussed until consensus was reached (Figure 1).

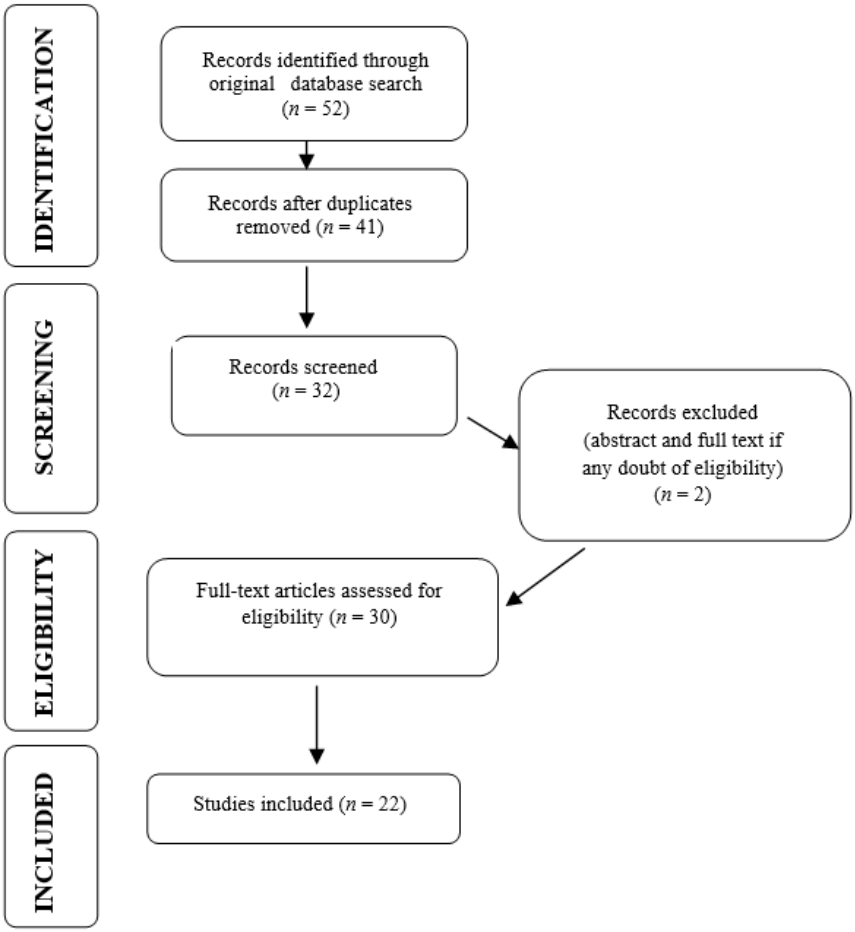

Figure 1. PRISMA flow diagram for research stages.

2.4. Inclusion Criteria

The inclusion criteria for the studies were as follows: studies investigating CO_2 laser excision of benign/potentially malignant lesions, erythroplakia, and leucoplakia which did or did not degenerate into SCC, studies reporting clinical series of patients with oral leucoplakia compared to other therapies, clinical studies that included the follow-ups of the subjects included, systematic reviews, and meta-analyses.

2.5. Exclusion Criteria

The exclusion criteria were as follows: duplicated studies, animal studies, experimental laboratory studies, case reports, intra-lesion treatment, phototherapy, CO_2 laser therapy in combination with other types of laser treatments, and clinical studies on subjects younger than 18 years old.

2.6. Data Collection and Analysis

From each selected study, the following information was collected, when possible: first author, year, number of patients treated with CO_2 laser therapy, type of oral lesion, recurrence rate, malignant transformation rate, the outcomes, and the complication rates.

3. Results

Initially, the search identified 52 articles. The primary analysis of the titles and abstracts eliminated 22 articles, leaving 30 articles whose full texts were examined. A total of 22 articles met the inclusion criteria (Figure 1). The studies were classified into three categories:(1) CO_2 Laser Treatment in the Case of Oral Leukoplakia, (2) CO_2 Laser Treatment in the Case of Oral erythroplakia, (3) CO_2 Laser Treatment in the Case of Oral

Lichen Planus. The main outcomes of the clinical studies included in this review were introduced in Table 1.

3.1. CO_2 Laser Treatment in the Case of Oral Leukoplakia

In a clinical study published by Singh et al. (2016), 32 patients with 44 oral leukoplakia lesions were treated using CO_2 laser vaporization. The follow-up period was 6–12 months, and some etiological factors (smoking, alcohol consumption, dental trauma, etc.) were also recognized and eliminated if possible. While forty lesions (90.9%) achieved local control after one laser session, a rate of 97.7% was obtained after the second or third vaporization. The recurrence rate was 9.10% and one case (2.27%) suffered from malignant transformation after CO_2 laser surgery [32].

A clinical trial published by Romeo et al. (2020) investigated the efficiency of CO_2 laser ablation of oral leukoplakia on 30 patients (with a total of 33 oral leukoplakia lesions). The lesions were divided into three groups for study, as follows: (A) 11 lesions in 11 patients, for which the laser ablation was performed for the entire lesion without extension of margins; (B) 11 lesions in 8 patients, for which ablation was done with a minimum extension of 3 mm of margins; (C) 11 untreated lesions in 11 patients with no treatment approach, with a periodic 6-month follow-up. The results revealed complete healing of 13 lesions in Groups A and B, and complete regression in the case of three lesions in Group C. However, 6 out of 9 lesions in Groups A and B that showed recurrence after 6 months also showed initial recurrence after 3 weeks of laser ablation. Complete healing occurred in 87.5% of patients with no smoking history, while for ex-smoker patients, complete healing was observed in 42.8%. With overall recurrence rates of 45.5% in Group A and 36.4% in Group B, the authors concluded that the recommended extension of the margins should be at least 3 mm in width [33].

A retrospective study published by Yang et al. [34] assessed the demographic data and pathological results of 111 patients (80 males and 31 females) who underwent CO_2 laser surgery for tongue leukoplakia between 2002 and 2019. The results showed that the prevalence of ventro-lateral tongue leukoplakia was higher than that of dorsal tongue leukoplakia ($p < 0.001$). The follow-up time was 3.74 ± 4.19 years. Fifteen patients had postoperative recurrence (13.51%), while four patients (3.6%) developed malignant transformation. The authors concluded that, while dorsal tongue leukoplakia was not as frequently encountered clinically as ventro-lateral tongue leukoplakia, the therapeutical outcomes were comparable among the two types of lesions, in terms of postoperative recurrence and postoperative malignant transformation.

Yang et al. [35] performed a retrospective study on elderly patients (older than 65 years) suffering from oral leukoplakia (OL) who received surgical excision of OL lesions with CO_2 laser. A total of 69 subjects were included in the study, with a mean age of 71.2 ± 4.9. The univariate statistical analysis revealed that some factors, such as morphology, pathology, and area of the lesion, were associated with postoperative recurrence. In the multivariate logistic regression model, the lesion's pathology and area were predictive factors for recurrence. Malignant transformation occurred in eight subjects (11.6%).

Kshirsagar et al. (2020) performed a study on 20 patients (44 oral leukoplakia lesions) treated with CO_2 vaporization, with a follow-up of 6 to 12 months (a mean of 9 months). Their results revealed that forty lesions were considered cured after the first laser session, two lesions were cured after the second session, and one lesion was considered treated after the third session. The rate of recurrence was 2.27% (one case) for this study [36].

In order to assess the treatment outcomes of the CO_2 laser compared with traditional cold knife surgery, three studies were selected. Huang et al. [37] guided a retrospective study, which included 73 patients with vascular malformations, oral leukoplakia, and verrucous nevus. In the study group, 53 patients were treated with CO_2 laser, while the remaining 20 patients received classic surgery and were considered to be the control group. Comparing the outcomes, the study revealed that the operating times were shorter and bleeding was less in the laser group than in the control group.

Another two prospective studies (Lopez-Journet et al. [38] and Tambuwala et al. [39]) also compared and evaluated CO_2 laser interventions with conventional surgery. Lopez-Journet et al. conducted a randomized clinical trial from January 2005 to December 2010 and included 48 patients with a mean age of 53.7 years (ranging from 28 to 74 years), all suffering from oral leukoplakia. A total of 39 were smokers, while 9 were non-smokers. The study's main conclusion was that postoperative pain and edema were dependent on the size of the lesion.

Tambuwala et al.'s study [39] consisted of 30 patients with bilateral oral leukoplakia lesions, thus resulting in 60 oral leukoplakia cases. Their main results included less postoperative swelling, less hemorrhaging, less postoperative scarring (after 1 month), less pain, and a shorter excision time when the CO_2 laser was used.

Currently, in the case of oral leukoplakia lesions, several therapies can be used in order to prevent malignant transformation, such as surgical treatment (cold knife surgery, cryotherapy, or laser treatment) or drug therapy (vitamin A and retinoid, non-steroidal anti-inflammatory drugs, or even herbal extracts). However, there is no therapy able to prevent the recurrence or significantly reduce malignant development in long-term follow-up studies [40].

Brouns et al.'s study [41] involved 35 oral leukoplakia patients that were treated using the CO_2 laser. Follow-ups occurred between 12 and 179 months. A total of 35 patients presented recurrences in the first 43 postoperative months. Later on, after a 54-month period, malignant transformations had developed in five cases.

Modegas et al. [42] conducted a retrospective study of 65 patients suffering from oral leukoplakia. The patients were treated using CO_2 laser and subsequently followed up for 15 months. A total of 22 patients were identified as recurrent cases during this time, while 10 patients presented with malignant transformations.

Dong et al. [43] published a meta-analysis investigating the malignant transformation of oral leukoplakia lesions treated with CO_2 laser. Based on the 24 studies included in the research, the authors concluded that non-invasive treatment options should be first considered in the case of oral leukoplakia patients. In addition, the results of this meta-analysis revealed that the overall rate of malignant transformations of the oral lesions is 4.5%.

Another meta-analysis published by Pauli Paglioni et al. investigated the malignant transformation of oral leukoplakia lesions treated either by classic surgical techniques or by different laser surgery (Nd: YAG, Er: YAG, CO_2, or diode laser). The authors concluded that the overall rates of recurrence and malignant transformation for oral leukoplakia lesions treated by surgical laser were 16.5% and 5.2%, respectively. In comparison to classic surgery excision, laser ablation seems to have a lower recurrence rate, but it does not seem to affect the rate of malignant transformation in oral leukoplakia patients [44].

Natekar et al.'s comparative study [45] focused on 30 patients divided into three study groups; the first group was treated with a diode laser, the second group received CO_2 laser treatment, and the third group was treated using cryosurgery. The results displayed important differences in parameters, such as swelling, pain, and scar formation, but less significant differences for postoperative infection, lesion recurrence, and bleeding. The Visual Analogue Scale (VAS) was used for pain analysis, and the greatest pain was found in the CO_2 laser group when compared to the diode laser group in the days following surgery. Meanwhile, on the same day as the intervention, the VAS for pain reported the highest values in the cryosurgery group. No lesion recurrences were reported in any of the groups.

In a meta-analysis published by Rui Liu et al. [46], the clinical effects of Er: YAG laser and CO_2 laser in the treatment of oral tumorous lesions were assessed. The authors performed a comprehensive search of studies conducted between 2000 and 2019. The results of six studies involving 268 patients met the study's eligibility criteria. The meta-analysis revealed that Er: YAG laser had better effects than CO_2 laser in eliminating oral leukoplakia lesions. However, Er: YAG laser needed a longer operation time compared

to CO_2 laser. The recurrence and complications of the CO_2 and Er: YAG groups had no significant difference.

3.2. CO_2 Laser Treatment in the Case of Oral Erythroplakia

Yang et al. (2014) designed a study in order to analyze the outcomes of treatment in patients with oral erythroplakia. A total of 84 patients were enrolled in the research, all of them treated with CO_2 laser vaporization. The mean follow-up period was 46 months, and the postoperative recurrent rate was 14 out of 84 cases (16.7%). The authors concluded that laser surgery was effective in the case of oral erythroplakia, However, the postoperative recurrence seemed to be associated with the size of the area of the lesion (lesions larger than 80 mm^2 were a significant predictive factor of postoperative recurrence) [47].

Jerjes et al.'s studies [48,49] used CO_2 laser treatment for patients with homogeneous leukoplakia, non-homogeneous leukoplakia, and erythroplakia. The mean age was 58 years and follow-ups extended to a mean period of 6.4 years. Moderate dysplasia developed in 42 patients, while severe dysplasia occurred in 18 patients. They concluded that the recurrence rate was 19.5% and malignant transformation took place in 10.4% of cases.

It was noted that the recurrence rate seemed to depend on the degree of epithelial dysplasia, while smoking and alcohol consumption also played a significant part. Higher recurrence rates were observed in erythroplakia lesions and in cases of non-homogeneous leukoplakia.

Another clinical study, published by Thomas et al. [50], was performed on 30 patients with a diagnosis of potentially malignant lesions (leukoplakia, erythroplakia), in situ carcinomas, or T1/T2 squamous cell oral carcinoma. The outcomes of the CO_2 laser ablation were assessed, such as intraoperative blood loss, length of hospital stay, postoperative pain, time to re-epithelization, pathological margins attained, and postoperative evolution, including functional outcome and recurrence rate after 1 year post-treatment. The authors concluded that CO_2 laser ablation was beneficial in the management of premalignant lesions as well as low-risk T1/T2 tumors of the oral cavity, with specific advantages related to rapid re-epithelization and minimal intraoperative blood loss, minimum postoperative pain as well as minimum functional impairment. After 1 year post-treatment, none of the subjects developed local recurrence; however, one patient had lymph node recurrence.

Saibene et al. (2019) published a systematic review with the aim of evaluating the outcomes of laser surgery over a wide range of lesions (oral leukoerythroplakia, oral leukoplakia, oral dysplasia, etc.) as well as to provide a solid and reproducible protocol for CO_2 laser surgery. The outcomes of their investigations were that CO_2 laser surgery is effective for a wide range of oral lesions [51].

3.3. CO_2 Laser Treatment in Case of Oral Lichen Planus

In a clinical study published by Agha Hosseini et al. (2012), 28 patients (with 57 oral lichen planus lesions) were randomly divided into two groups and treated with either low-level laser therapy (LLLT) or CO_2 laser surgery. After 3 months, the clinical response showed 100% partial to complete improvement in the case of LLLT, and 85% in the case of CO_2 laser surgery. Thus, the results revealed that LLLT may be superior to CO_2 laser therapy [52].

Mucke et al. (2014) performed a clinical trial in order to analyze the impact of defocused CO_2 vaporization on the malignant transformation of erosive oral lichen planus (erosive OLP). With the participation of 171 patients with erosive OLP, the study demonstrated that some factors (such as symptomatic analgesic treatment in the case of erosive OLP) have significantly higher risk associated with the occurrence of malignant transformation. The authors emphasized the potential impact of the CO_2 laser in the management of patients with erosive OLP [53].

Matsumoto et al. (2019) evaluated the efficacy of CO2 laser vaporization therapy on refractory to conservative treatments for oral lichen planus (OLP). A total of 16 patients with clinically and histologically diagnosed OLP underwent conservative treatment for

3 months (adrenal cortex hormone ointment and azulene sulfonate sodium hydrate gargle). Patients who showed no improvement with conservative treatment underwent CO_2 laser vaporization therapy (3 W, continuous-wave mode). The numerical rating score (NRS) decreased at all 11 sites (100%) and 10 sites (90.9%) at 1 year after irradiation, compared to pre-irradiation scores [54].

Table 1. Clinical studies included in the present research.

Author	Study Type	Participants	Intervention	Outcomes
Jerjes et al. (2012) [31]	Retrospective study	77 patients with 123 oral dysplastic lesions, mean age of 58 years	CO_2 laser treatment, mean follow-up at 6.4 years	Normal recovery, no complications. Recurrence rate 19.5%. Malignant transformation in 8 patients.
Lopez-Journet et al. (2012) [38]	Prospective study	48 patients, mean age of 53.7 years with oral leukoplakia	Group 1: standard cold knife technique, including 3 mm of clinically normal mucosa at periphery; Group 2: CO_2-laser, including 3 mm of clinically normal mucosa at the periphery; mean follow-up at 27.9 months	Pain and swelling increased in conventional cold knife approach. Group 1: peak pain intensity at 12 h postoperatively, peak swelling scores at 24 h after surgery. Group 2: peak pain at 12–24 h postoperatively; peak swelling at 12–48 h postoperatively; no malignant transformation during the follow-up period.
Agha-Hosseini et al. (2012) [52]	Clinical trial	28 patients with oral lichen planus lesions	2 groups, Group 1: low-level laser therapy, Group 2: CO_2 laser therapy	Low-level laser therapy showed superior results compared to CO_2 laser.
Brouns et al. (2013) [41]	Retrospective study	35 patients with oral leukoplakia	CO_2 laser vaporization, mean follow-up at 61.9 months	35 patients had benign recurrences in the first 43 months; 5 patients had malignant developments within 54 months.
Tambuwala et al. (2014) [39]	Prospective study	30 patients with (60) bilateral oral leukoplakia lesions	Group 1: CO_2 laser excision, Group 2: scalpel excision	Group 2: increased intraoperative bleeding, increased edema, increased scarring 1 month postoperative, pain similar.
Yang et al. (2014) [47]	Retrospective study	84 patients with oral erythroplakia (mean follow-up at 46 months)	CO_2 laser excision	The postoperative recurrent rate was 14/84 (16.7%).
Huang et al. (2015) [37]	Retrospective study	77 patients with OL, Group 1: 47 patients, Group 2: 30 patients	Group 1: treated with laser evaporation using Nd: YAG laser, Group 2: treated with CO_2 laser for excision, mean follow-up at 60 months	22 patients with recurrence at follow-up. No significant difference between the groups.
Modegas et al. {2015) [42]	Retrospective study	65 patients with oral leukoplakia	CO_2 laser vaporization, Follow-up at 15 months	Recurrence in 22 patients; malignant transformation in 10 patients; complications in 5 patients.
Singh et al. (2016) [32]	Clinical study	32 patients (44 oral leukoplakia lesions)	CO_2 laser Vaporization, follow-up at 6–12 months	9.1% recurrence rate and 2.27% (1 case) malignant transformation rate after Co2 laser surgery.

Table 1. *Cont.*

Author	Study Type	Participants	Intervention	Outcomes
Natekar et al. (2017) [45]	Comparative study	30 patients with oral leukoplakia, mean age: 36 years, 6 weeks post-cessation of harmful habits (alcohol, tobacco, etc.)	Group 1: diode Laser, Group 2: CO_2-laser, Group 3: nitrous oxide cryosurgery, follow-ups at weeks 1 and 2 and months 3 and 6	Significant differences for edema, pain, and scar formation; no statistical difference for infection recurrence, bleeding.
Thomas et al (2018) [50]	Prospective observational study	30 patients with potentially malignant oral lesions (leukoplakia, erythroplakia, etc.), in situ cancers, or T1/T2 squamous cell carcinoma	CO_2 laser excision, outcomes of the CO_2 laser ablation were assessed	CO_2 laser is effective in the management of premalignant and low-risk T1/T2 tumors of the oral cavity.
Yang et al. (2019) [35]	Retrospective study	53 males and 16 females, mean age of 71.2 $\pm$ 4.9.	CO_2 laser surgery for oral leukoplakia (OL) from 2002 to 2017	The prognostic factors for postoperative recurrence of oral leukoplakia are pathological high-risk dysplasia and the area of OL.
Matsumoto et al. (2019) [54]	Prospective study	16 subjects with oral lichen planus	Laser administration for 11 lesions	CO_2 laser vaporization therapy was efficient for refractory oral lichen planus.
Romeo et al. (2020) [33]	Clinical trial	30 patients (33 oral leukoplakia lesions)	Group A: 11 lesions/11 patients, CO_2 laser ablation without safety margins, Group B: 11 lesions/8 patients, CO_2 laser ablation with a minimum of 3 mm safety margins; Group C: no treatment, "wait and see" approach	Complete healing in the case of 13 lesions; Recurrence in 9 subjects after a 6-month follow-up.
Kshirsagar et al. (2020) [36]	Clinical study	20 patients (44 oral leukoplakia lesions)	CO_2 laser vaporization, follow-up at 12 months	8 out of 20 patients treated for cure (90%) achieved local control after one session; the rate of malignant transformation after CO2 laser treatment was found to be 2.27%.
Yang et al. (2021) [34]	Retrospective study	111 patients, 80 males and 31 females, mean age of 51.86 $\pm$ 11.84 years	CO_2 laser surgery for oral leukoplakia lesions, follow-up at 3.74 $\pm$ 4.19 years.	Dorsal tongue leukoplakia is not as frequently encountered clinically as ventrolateral tongue leukoplakia. Clinicians should consider a more aggressive attitude towards tongue leukoplakia.

4. Discussion

After registering and presenting all outcomes of the above-mentioned studies, further discussion of these results is required. However, it is generally difficult to compare different

studies, given the alternating study parameters, the intermittently differing lesion types, and various study circumstances.

In the case of oral leukoplakia, when comparing CO_2 laser to classic surgery, the studies that were included in this review mainly concluded that shorter operating times, less bleeding, less pain, and less postoperative swelling were all advantages presented by the CO_2 laser, with emphasis on the bleeding and swelling parameters. Huang et al. [37] and Lopez-Journet et al.'s [38] studies may have a lower impact on our review due to the larger number of patients that received conventional surgery than those who were subjected to laser treatment. However, in Lopez-Journet et al.'s study, every procedure was carried out by the same surgeon, and detailed information about the interventions was provided, which in turn, increases the study's significance. Both approaches required the same amount of tissue to be removed, namely 3 mm of perilesional tissues were needed to be excised for recurrence prophylaxis. Therefore, equal invasiveness can be attributed to both approaches. However, CO_2 laser may be a more suitable choice since less postoperative scarring was also reported when compared to classical surgery.

Furthermore, when comparing the CO_2 laser to the diode laser and to cryosurgical therapy, the latter seems to have had the least positive results, including increased pain on the day of surgery, scar formation, increased postoperative pain, and swelling present even after a 2-week period. In contrast to these results, the patients that received the CO_2 and diode lasers only reported slight pain levels, which were higher in the CO_2 laser group, on the day of surgery and postoperatively.

When referring to lesion recurrence and malignant transformations of oral leukoplakia lesions, the main issue encountered in comparing these results was the extremely variable follow-up period (ranging from 2 to 102 months). A general consensus was attempted in order to obtain guidelines suitable for the clinical approach concerning lesion recurrence and malignant transformations. The average outcomes of our reviewed studies confirm that most of the patients' evolution was non-pathological. However, an average of 25% of patients did present with recurrent lesions during the follow-up period, while malignant developments and other complications were relatively low. When assessing such parameters, the lesion's location, grade of dysplasia, type, and the presence of risk factors, such as smoking, alcohol consumption, and the existence of previous malignancies, must be taken into account.

In the case of oral erythroplakia, only a few studies were published over the last decade. Yang et al. (2014) concluded that CO_2 laser surgery is effective as long as the lesion is confined to dysplasia of any degree, and that postoperative recurrence was associated with the size or the area (larger than 80 mm^2) [47]. Significant findings were also emphasized by Agha-Hossein et al. (2012) after performing their clinical trial, showing that low-level laser therapy might be more effective in the case of oral lichen planus lesions compared to CO_2 laser surgery [52].

Overall, the advantages of CO_2 laser include the precision of tissue removal and beam control (through the microscope), minimal damage of the surrounding tissues, as well as the immediate hemostatic effect, superior tissue healing, and the reduction in postoperative pain and tissue edema.

5. Conclusions

After evaluating the results of all the studies included in this review, an initial general statement can be made, namely that CO_2 lasers are a treatment option worth taking into consideration when approaching oral mucosal lesions. There is no medical treatment currently known that can ensure 100% disease-free recovery in the case of potentially premalignant oral epithelial lesions. However, there are therapies that, as has been outlined, generally cause fewer intra- and postoperative complications/side effects. Keeping in mind the invasiveness of the treatment itself, clinicians (oral or head and neck surgeons) should also consider the psychological aspect of therapy along with the biological/physical ones; all the previously discussed parameters—shorter treatment duration, less intra- and

postoperative pain, decreased swelling, and less scarring—come in favor of positive patient psychology, both for patients in search of treatment possibilities, as well as for outgoing patients. Nevertheless, the pathological interpretation of laser margins may be hampered by heat degradation to the margin. Therefore, a pathologist with experience in head and neck specialization would be an important member of the medical team. In addition, long-term follow-up programs should be implemented in order to detect malignant transformation in its early stages and to minimize cancer treatment morbidity and mortality rates.

It is our strong opinion that any oral lesions are carefully diagnosed by a specialist. Clinical and morpho-pathological diagnosis should be in place before starting any treatment. While surgery remains the gold standard, CO_2 laser therapy can be used in very well-defined cases. A careful follow-up is mandatory in order to prevent malignant complications. Based on our research, we can conclude that there is a need for further randomized clinical trials in order to evaluate the outcomes of CO_2 laser surgery compared to other treatment options, while multicenter studies could increase the relevance of statistical analysis. In addition, standardized recurrence criteria are required for an accurate evaluation of existing studies.

Author Contributions: Conceptualization, D.C. and A.K.; methodology, R.B. and S.B; software, I.Ț.; validation, S.B., R.B, and O.B.; resources, O.B.; writing—original draft preparation, S.B.; writing—review and editing, C.C.; visualization, I.Ț. and S.B.; supervision, A.K.; project administration, D.C and S.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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