Invited Review

Efficacy of surgical laser therapy in the management of oral pigmented lesions: A systematic review

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A R T I C L E   I N F O

Keywords:
- Laser therapy
- Oral pigmentation
- Gingiva
- Depigmentation
- Hyperpigmentation
- Systematic review

A B S T R A C T

Background: Oral pigmentation, especially in the gingiva poses esthetic problems. Laser therapy has been widely used for cosmetic therapy in dentistry. The aim of the present study was to systematically review the efficacy of surgical laser therapy (SLT) in the management of oral pigmented lesions (OPL).

Methods: The addressed focused question was “Is SLT effective in the management of OPL?” Databases (MEDLINE via PubMed; EMBASE; Cochrane Central Register of Controlled Trials and Cochrane Oral Health Group Trials Register databases) were searched from 1970 up to and including February 2017.

Results: Ten studies were included. The reported number of OPL ranged between 8 and 140. Oral pigmented sites included gingiva, buccal and labial mucosa, alveolar mucosa and lips. Lasers used in the studies included Q-switched alexandrite, Neodymium-doped yttrium aluminium garnet, diode, Erbium: yttrium aluminium garnet and carbon dioxide laser. Laser wavelength, power output and number of irradiations were 635–10,600 nm, 1–10 W and 1 to 9 times, respectively. The follow up period ranged from 6 to 24 months. All studies reported SLT to be effective in the treatment of OPL. In five studies, recurrence of OPL occurred which ranged from 21.4% to 45%.

Conclusions: Lasers are effective in the management of OPL including physiologic gingival pigmentation, smokers’ melanosis and pigmentation in Laugier–Hunziker syndrome. Different laser types (CO2, Er:YAG and Diode) showed comparable outcomes in the treatment of OPL.

1. Introduction

Surgical laser therapy (SLT) is a contemporary treatment option in the diagnosis and management of oral disorders [1]. Its mechanism is based on the premise that absorption of light by exposed tissues results in destruction and death of cellular structures due to high temperatures (Photothermolysis). As tissue absorption of light is dependent on specific light wavelength, targeted damage of selected pathological tissue is possible allowing selective photothermolysis of cells [2]. Laser therapy has shown promising outcomes in the management for a variety of oral diseases [3–8].

Oral pigmentation is discoloration of oral mucosa and gingiva associated with internal or external factors. Oral pigmentation can present as physiologic changes (racial), oral manifestation of systemic disorders (including Peutz-Jeghers syndrome and Addison's disease), habitual smoking and malignant neoplasms (such as Kaposi's sarcoma) [9,10]. Multiple causes are known to trigger pigmented lesions that include genetic aberration, inflammation, endocrine disturbances, drugs and smoking [8,10,11]. Activation of melanocytes in the basal and suprabasal layer of epithelium results in the formation of premelanosomes containing tyrosinase enzyme [12]. Oxidation of tyrosine through tyrosinase enzyme forms melanin pigment within melanosomes [13]. It is proposed that the physiological appearance of oral mucosa is due to the transfer of melanosomes into the keratinocytes [12,14]. Increased stimulation and activity of melanocytes due to local and systemic factors causes increased formation and deposition of melanin pigment resulting in hyperpigmentation [15].

Various therapeutic strategies have been proposed for the management of oral pigmented lesions (OPL) including epithelial abrasion, scalpel surgery, electrosurgery, cryosurgery, gingival grafts and
chemical cauterization [16–18]. Surgical techniques conventionally used for depigmentation results in elimination of pigmentation from the epithelial and connective tissue, however, these are associated with pain, bleeding and discomfort during the healing period [18,19]. Non-surgical treatment strategies (such as application of cryogen and epithelial abrasion) for the management of OPL may be successful in the short-term; however such therapeutic methods have shown recurrence of lesions in the long term [16].

A variety of lasers have been used in the management of OPL [20,21]. In a study by Soliman et al. [20], 20 patients with OPL on the buccal mucosa and gingiva were treated using diode laser. The results showed complete resolution of OPL with no recurrence up to 9 months of follow up. Similarly, in a 1 year follow up study by Zuo et al., [21] oral pigmented lesions were effectively eliminated using Alexandrite laser in 22 patients. The above results suggest that SLT may be a potential treatment strategy for the management of OPL. However, Kishore et al., [22] in a recent study reported a recurrence rate of up to 40% for OPL treated with Er:YAG laser. Similarly, Ribeiro et al. [23] reported a 45% recurrence of OPL at up to 6 months follow up. Therefore, there appears to be a controversy with regard to the effectiveness of SLT in the management of OPL; and to our knowledge from indexed literature, the efficacy of SLT in the management of OPL has not been systematically reviewed. Therefore, the aim of the present study was to systematically review the efficacy of SLT in the management of OPL.

2. Materials and Methods

2.1. Protocol and Registration

This review was registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO), registration number: CRD42016239927). Based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, [24] a focused question was constructed. The addressed focused question was: “Is SLT effective in the management of OPL?”

2.2. Eligibility Criteria

Two reviewers (FV and ZA) independently screened titles and abstracts for eligible papers. Any disagreement involving the eligibility was resolved through discussion. Studies which did not fulfill the inclusion criteria were excluded. The following eligibility criteria were entailed: Study design: Both randomized controlled trials (RCTs) and non-RCTs were included; Participants: patients with OPL without systemic disease; Intervention: subjects allocated to experimental group based on having SLT; Outcome: studies reporting resolution of pigmented lesions were included as cosmetic outcomes; Follow-up: the outcome assessment at minimum of 6 months and; articles published only in English language. Review articles, experimental studies, case-reports, commentaries, case series, letters to the Editor and unpublished articles were excluded.

2.3. Search Strategy

The authors searched the main databases (MEDLINE via PubMed; EMBASE; Cochrane Central Register of Controlled Trials and Cochrane Oral Health Group Trials Register databases) from 1970 up to and including February 2017 for appropriate articles addressing the focused question. Reference lists of original studies were manually searched to identify any articles that could have been missed during the initial search. Manual searching of the following journals was performed: Oral Surg Oral Med Oral Pathol Oral Radiol; Lasers Med Sci; Arch Dermatol Res; J Periodontol; Oral Surg Oral Med Oral Pathol Oral Radiol Endod; Int J Health Sci; Oral Health Dent Manag; and Lasers Surg Med. Any disagreements regarding study selection were resolved via discussion. Electronic database searches were performed using different combinations of the following Medical Subject Heading (MeSH) and text words: lasers [MeSH]; esthetics [MeSH]; oral pigmentation [Text word]; melanins [MeSH]; depigmentation [Text word]; gingival pigmentation [Text word]; and treatment [Text word].

2.4. Screening Methods and Data Abstraction

Titles and abstracts of articles that satisfied the selection protocol were screened and checked for agreement. The information from the accepted studies were tabulated according to the study design; demographic characteristics of the participants; study groups; site and number of pigmented lesions; their follow up; recurrence; study outcome; quality of the studies and laser characteristics. Agreement between the two reviewers with regard to the study selection procedure was calculated using Cohen’s kappa (κ) statistics at initial screening of the titles and final full-text eligibility.

2.5. Risk of Bias in Individual Studies

The quality assessment of the included RCTs was assessed based on the revised recommendations of the Consolidated Standards of Reporting Trials statement (CONSORT) [25]. The risk of bias was estimated for each selected RCT based on the Cochrane Handbook for Systematic Reviews of Interventions; [26] 1) low risk of bias (when all criteria were met); 2) moderate risk of bias (when ≥1 criterion was partially met); and 3) high risk of bias (when ≥1 criterion was not met). The risk of bias for non-RCTs was assessed using modified version of the Downs and Black checklist [27].

2.6. Statistical Analysis

Due to the lack of methodological uniformity of the included studies, no meta-analysis could be performed and the outcomes are presented as a narrative review.

3. Results

3.1. Study Selection

A total of 56 study titles and abstracts were initially identified. After removal of the duplicates (n = 3), a total of 53 articles were eligible for initial screening. After initial screening of 53 titles and abstracts, 36 articles were excluded as irrelevant to the focus question (κ score for inter-assessor agreement [95% Confidence Interval]: 0.91 [0.85–0.97]). A total of 17 papers were selected for full-text reading. Of these 17 studies, 7 studies were further excluded (Fig. 1). After the final stage of selection, 10 studies [20–23,28–33] were included and processed for data extraction (κ score for inter-assessor agreement [95% Confidence Interval]: 0.84 [0.78–0.92]). All studies [20–23,28–33] were performed at either universities or health care centres. Fig. 1 shows the study identification flow chart according to PRISMA [24] with the reasons for exclusion of articles.

3.2. General Characteristics of the Studies

All studies [20–23,28–33] were prospective clinical trials. The total number of patients ranged between 8 and 35 individuals. All studies [20–23,28–33] reported the number of female participants, which ranged between 2 and 20 individuals. Five studies [20,21,23,28,33] reported the mean age of study participants, which ranged between 25.6 years and 42.4 years (age range 18 to 74 years). The total number of OPL was reported in three studies, [21,29,31] which ranged between 8 and 140. All studies [20–23,28–33] reported the site of lesions, which included gingiva, buccal and labial mucosa (maxilla and mandible),
alveolar mucosa and lips (maxilla and mandible) (Table 1).

In 8 studies, [20–22,28,30–33] SLT was used as the sole treatment strategy for the management of OPL. In studies by Ribeiro et al. [23] and Hegde et al., [29] efficacy of SLT was compared with scalpel surgery and surgical stripping (control groups). In three studies, [22,29,33] Dummett Oral Pigmentation Index (DOPI) and Hedin melanin index were used to assess the extent of pre and post-operative oral pigmentation. The follow up period ranged from 6 months to 24 months (Table 1).

In 7 studies, [20–23,29,30,32] subject included were systemically healthy and non-pregnant. In five studies, [21,22,29,30,33] OPL were diagnosed using histopathology. In nine studies [20,22,23,28–33] subjects with physiologic gingival pigmentation were included. In the study by Zuo et al., [21] recruited patients with OPL due to Langer-Hunziker syndrome (LHS). Patients were excluded with oral pigmentation due to systemic disorders in the included studies [20–23,28–33]. In 3 studies, [22,23,29] oral hygiene of the patients was reported to be satisfactory and was maintained throughout the trial. In 4 studies, [21,28,30,33] smokers (ranging between 2 and 19 individuals) were also included. One study [28] reported the frequency of smoking, which was > 10 cigarettes per day (for all smokers).

3.3. Laser Related Parameters of Included Studies

One study used Q-switched alexandrite [21] (QSAL) and Nd:YAG [23] (neodymium-doped yttrium aluminium garnet) laser respectively. Diode laser was used in 2 studies, [20,28] Er:YAG (Erbium-yttrium aluminium garnet) laser in 4 studies [22,28,29,32] and CO2 laser was used in 5 studies [22,29–31,33]. In 8 studies, [20–22,28–30,32,33] wavelength of lasers was reported which ranged from 635 to 10,600 nanometers (nm). Eight studies [20,22,23,28–31,33] reported power output of lasers which ranged between 1 W (watts) to 10 W (Table 2). All studies [20–28–33] reported the number of irradiation sessions, which ranged from 1 to 9 times. Pulse energy and energy density was reported by 4 [22,23,29,32] and 3 [20,21,33] studies, which were 60 mJ/pulse (millijoules/pulse) to 500 mJ/pulse and 5 J/cm² (joules per centimeter square) to 12 J/cm² respectively. In 5 [20,21,30,32,33] and 4 [20,23,28,33] studies, laser spot diameter and fibre diameter were 2 mm (millimeters) to 4 mm and 200 µm (micrometers) to 1000 µm respectively.

3.4. Outcomes of Included Studies

In only 2 [23,29] out of 10 studies, [20–23,28–33] efficacy of SLT in the management of OPL was compared to surgical treatment (control group). In the study by Ribeiro et al., [23] cosmetic outcomes for OPL among laser treatment and surgical therapy were comparable whereas in the study by Hegde et al., [29] surgical treatment showed significantly better cosmetic outcomes as compared to SLT in the treatment of OPL. In the included studies, [20–23,28–33] the reported unwanted effects of SLT included mild pain, mild edema, erythema, burning sensation and burning odor. However these untoward effects were short lived (up to 1 week) and did not cause functional interference for patients. In all studies, [20–23,28–33] SLT was found effective in the treatment of OPL. In all studies, [20–23,28–33] recurrence of OPL ranged between 0 and 45% at follow up.

The authors were unable to perform a meta-analysis due to heterogeneity in the presented data. Firstly, in 4 studies, [22,23,28,29] the efficacy of laser in the treatment of oral pigmentation was compared to other lasers [22,28] or to surgical treatment, [23,29] however, in the remaining six studies, [20,21,30–33] no comparisons of laser treatment were made as there were no controls. Secondly, 4 studies presented outcomes with means and standard deviations [22,23,28,29], while 6 studies [20,21,30–33] presented results in the form of either frequency or number of pigmented lesions or merely presence and absence of lesions before and after treatment. For this reason it is impossible to compare and combine the outcomes of these studies and use them for statistical analysis.

3.5. Quality of the Clinical Studies

Four clinical studies [22,23,28,29] in this systematic review were RCTs whereas 6 studies were non-RCTs [20,21,30–33]. Randomization was performed by either computer-generated random numbers, [22,23] or coin toss [29]. All RCTs [22,23,28,29] did not report sample size calculation whereas 3 studies [22,23,28] did not report masking of assessors. All RCTs [22,23,28,29] were regarded as low quality studies. Out of 6 non-RCTs, [20,21,30–33] three non-RCTs [20,30,31] were considered to have a high risk of bias, 2 studies [21,33] low risk of bias whereas one study [32] had moderate risk of bias (Table 3).

Fig. 1. PRISMA flow diagram for studies retrieved through the searching and selection process.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study type</th>
<th>Number of patients; mean age in years (range)</th>
<th>Gender (female)</th>
<th>Test group</th>
<th>Control group</th>
<th>Pigmented lesion Site</th>
<th>Follow up (months)</th>
<th>Recurrence rate (%)</th>
<th>Study outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliman et al. [20]</td>
<td>Non-RCT</td>
<td>20; 27.5 (18–37)</td>
<td>20</td>
<td>OP patients treated with laser ablation</td>
<td>None</td>
<td>Buccal mucosa; gingiva</td>
<td>NA</td>
<td>Up to 9</td>
<td>All lesions showed 100% resolution of pigmented lesions at follow up.</td>
</tr>
<tr>
<td>Ribeiro et al. [23]</td>
<td>RCT</td>
<td>11; 39.82 (20–51)</td>
<td>7</td>
<td>OP treated with Nd:YAG laser ablation</td>
<td>OP treated with surgery</td>
<td>Gingiva</td>
<td>NA</td>
<td>Up to 6</td>
<td>Cosmetic outcomes in test and control groups at follow up were comparable.</td>
</tr>
<tr>
<td>Kishore et al. [22]</td>
<td>RCT</td>
<td>20; NA (18–30)</td>
<td>10</td>
<td>Group 1: OP treated with Er:YAG laser</td>
<td>Group 2: OP treated with CO2 laser</td>
<td>None</td>
<td>Up to 6</td>
<td>Group 1: 40</td>
<td>Cosmetic outcomes in both groups at follow up were comparable.</td>
</tr>
<tr>
<td>Hegde et al. [29]</td>
<td>RCT</td>
<td>35; NA (18–50)</td>
<td>20</td>
<td>Group 1: OP treated with CO2 laser</td>
<td>Group 2: OP treated with surgical stripping</td>
<td>Gingiva</td>
<td>140</td>
<td>Up to 6</td>
<td>Group 1: 22.8; Group 2: 28.6; Control: 21.4</td>
</tr>
<tr>
<td>Simsek Kaya et al. [28]</td>
<td>RCT</td>
<td>20; 25.65 (18–36)</td>
<td>13</td>
<td>Group 1: OP treated with Diode laser</td>
<td>None</td>
<td>Gingiva</td>
<td>NA</td>
<td>Group 1: 0</td>
<td>Cosmetic outcomes in both groups at follow up were comparable.</td>
</tr>
<tr>
<td>Zuo et al. [21]</td>
<td>Non-RCT</td>
<td>22; 42.4 (18–74)</td>
<td>18</td>
<td>OP treated with QSAL</td>
<td>None</td>
<td>Gingiva; buccal mucosa; lips</td>
<td>73</td>
<td>Up to 12</td>
<td>QSAL was effective in the cosmetic treatment of OP.</td>
</tr>
<tr>
<td>Esen et al. [30]</td>
<td>Non-RCT</td>
<td>10; NA (20–38)</td>
<td>8</td>
<td>OP treated with CO2 laser</td>
<td>None</td>
<td>Gingiva</td>
<td>NA</td>
<td>Up to 24</td>
<td>CO2 laser was effective in cosmetic treatment of OP.</td>
</tr>
<tr>
<td>Tal et al. [32]</td>
<td>Non-RCT</td>
<td>10; NA (20–38)</td>
<td>2</td>
<td>OP treated with Er:YAG laser</td>
<td>None</td>
<td>Gingiva</td>
<td>NA</td>
<td>Up to 6</td>
<td>ErYAG laser was effective in the cosmetic treatment of OP.</td>
</tr>
<tr>
<td>Ozbayrak et al. [31]</td>
<td>Non-RCT</td>
<td>8; NA (28–63)</td>
<td>4</td>
<td>OP treated with CO2 laser</td>
<td>None</td>
<td>Gingiva; buccal muossa; alveolar muossa; lips</td>
<td>8</td>
<td>Up to 18</td>
<td>CO2 laser was effective in the cosmetic treatment of OP.</td>
</tr>
<tr>
<td>Nakamura et al. [33]</td>
<td>Non-RCT</td>
<td>10; 29 (20–49)</td>
<td>4</td>
<td>OP treated with CO2 laser</td>
<td>None</td>
<td>Gingiva</td>
<td>NA</td>
<td>Up to 24</td>
<td>CO2 laser was effective in the cosmetic treatment of OP.</td>
</tr>
</tbody>
</table>


a. Split-mouth study design; same patients received both treatments on at different sites.
b. One site treated with CO2 laser, one with Er:YAG laser, and two with the surgical stripping, for each patient.
4. Discussion

In the present study, we reviewed pertinent literature with reference to the efficacy of SLT in the management of OPL. All studies [20–23,28–33] that fulfilled our eligibility criteria demonstrated that SLT is effective in the management of OPL. Although results from the studies included reflected that lasers are effective in the treatment of OPL, from the literature reviewed, the laser-related parameters markedly varied among the studies [20–23,28–33]. For instance, different types of laser sources (QSAL, Nd:YAG, Diode, Er:YAG and CO2) were used for treating pigmented lesions. It is well-known that the efficacy of LT depends on the utilization of specific wavelength in pigmented lesions [34] and it is also noted that there was a significant heterogeneity in the wavelength used in the included studies, ranging from 635 nm to 10,600 nm [20–23,28–33]: this factor might be responsible of an alteration of the present study outcomes. Almost 90% of the included studies [20,21,22,28–33] recruited subjects with physiologic pigmentation and found comparable results. Hence, the role of specific wavelength in the treatment of oral pigmented lesions is still unclear. Moreover, parameters such as laser fibre diameter, energy density and pulse energy were reported in six, [21,22,29–32] three [20,21,33] and five [20,21,30,32,33] studies respectively. Laser fibre diameter is known to be critical in the efficacy of SLT and has been reported to influence the energy density and energy output of the laser used [35]. Increasing the fibre diameter, increases the area of tissue surface, however reduces the amount of energy dispensed to target tissues [36]. In case of large fibre diameter, increasing the power, results in higher amount of energy delivered to tissues, leading to destruction of desired cells [36]. In the present systematic review, the size of pigmented lesions was not reported. In addition, the severity (mild to severe) and extent (pigmented spots to complete band formation) of OPL using a standardized classification (Dummett oral pigmentation index (DOPI) and Hedin melanin index) was only reported in three studies, [29,32,33] suggesting that the lesions varied among included studies [20–23,28–33]. Therefore, it is possible that the variation in laser parameters among the studies could have been adjusted with reference to the severity and extent of the oral pigmentation. Hence it seems difficult to standardize the laser parameters in the management of OPL.

It is noteworthy that 50% of the studies [22,23,29,30,33] included in the review reported recurrence of OPL after laser treatment, which ranged from 20% to 45%. Recurrence of physiologic pigmented lesions is associated with migration of melanocytes form adjacent tissues. Recurrence rates can vary with regards to the type of laser and duration of follow-up [29,33]. Ultraviolet light exposure, smoking, genetic and ethnic factors and hormonal influence can promote recurrence of pigmented lesions [37,38]. In the present review, an interesting association was observed between the recurrence rate of the pigmented lesions and the number of times the lesions were exposed to laser irradiation (1 to 9 times). Except one study [33], all studies [20,21,28,32] included in the present review in which laser irradiation was performed more than once, no recurrence of pigmented lesions was found up to 12 months of follow up. In the study by Nakamura et al. [33] OPL were exposed to laser irradiation for up to five times, however the recurrence rate was

Table 2
Laser parameters of the included studies.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Source</th>
<th>Wavelength (in nm)</th>
<th>Energy density (J/cm²)</th>
<th>Power output (W)</th>
<th>Number of irradiations</th>
<th>Fiber diameter (μm)</th>
<th>Pulse energy (mJ/pulse)</th>
<th>Spot diameter (in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliman et al.</td>
<td>Diode laser</td>
<td>803–813</td>
<td>5–15</td>
<td>1–2</td>
<td>Up to 3</td>
<td>400</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Ribeiro et al.</td>
<td>Nd:YAG laser</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
<td>1</td>
<td>320</td>
<td>60</td>
<td>NA</td>
</tr>
<tr>
<td>Kishore et al.</td>
<td>Group 1: Er:YAG laser</td>
<td>Group 1: 2940</td>
<td>NA</td>
<td>Group 1: 1.8</td>
<td>1</td>
<td>NA</td>
<td>Group 1: 180</td>
<td>NA</td>
</tr>
<tr>
<td>Hegde et al.</td>
<td>Group 1: CO2 laser</td>
<td>Group 1: 10,600</td>
<td>NA</td>
<td>Group 1: 1.8</td>
<td>1</td>
<td>NA</td>
<td>Group 2: NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hegde et al.</td>
<td>Group 2: Er:YAG laser</td>
<td>Group 2: 2940</td>
<td>NA</td>
<td>Group 2: 2–4</td>
<td>1</td>
<td>NA</td>
<td>Group 1: 180</td>
<td>NA</td>
</tr>
<tr>
<td>Hegde et al.</td>
<td>Group 2: CO2 laser</td>
<td>NA</td>
<td>NA</td>
<td>Group 2: 1</td>
<td>Up to 9</td>
<td>Group 1: 300</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hegde et al.</td>
<td>Group 2: Er:YAG laser</td>
<td>Group 2: 2940</td>
<td>NA</td>
<td>Group 2: 1</td>
<td>Up to 9</td>
<td>Group 2: 1000</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zuo et al.</td>
<td>Q-switched alexandrite</td>
<td>752</td>
<td>6.7</td>
<td>NA</td>
<td>Up to 6</td>
<td>NA</td>
<td>NA</td>
<td>2.4</td>
</tr>
<tr>
<td>Zuo et al.</td>
<td>laser (QSAL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esen et al.</td>
<td>CO2 laser</td>
<td>10,600</td>
<td>NA</td>
<td>10</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>0.8</td>
</tr>
<tr>
<td>Tal et al.</td>
<td>Er:YAG laser</td>
<td>635</td>
<td>NA</td>
<td>NA</td>
<td>Up to 2</td>
<td>NA</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td>Ozbayrak et al.</td>
<td>CO2 laser</td>
<td>NA</td>
<td>NA</td>
<td>5–7</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nakamura et al.</td>
<td>CO2 laser</td>
<td>10,600</td>
<td>9.6–12</td>
<td>6–8</td>
<td>Up to 5</td>
<td>200</td>
<td>NA</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3
Assessing the risk of bias in the included studies.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Sample size calculation</th>
<th>Allocation concealment</th>
<th>Randomization</th>
<th>Losses (withdrawals/dropouts)</th>
<th>Masking of assessor(s)</th>
<th>Appropriate statistical analysis</th>
<th>Estimated risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribeiro et al. [23]</td>
<td>0</td>
<td>2 comp gen</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>High</td>
</tr>
<tr>
<td>Kishore et al. [22]</td>
<td>0</td>
<td>2 comp gen</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>High</td>
</tr>
<tr>
<td>Hegde et al. [29]</td>
<td>0</td>
<td>2 coin toss</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>High</td>
</tr>
<tr>
<td>Simeek Kaya et al.</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<td>Soliman et al. [20]</td>
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<td>Zuo et al. [21]</td>
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<td>Esen et al. [30]</td>
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<td>Tal et al. [32]</td>
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* Risk of bias estimated by Modified Downs’ and Black checklist [27].
40% at 24 months follow up. An explanation in this regard may be derived from the fact that all patients who showed recurrence of pigmented lesions at 24 months follow ups were smokers. Therefore it is possible that if the number of laser irradiations were increased in the studies [22,23,29,30,33] showing recurrence of pigmented lesions in the present review, the pigmented lesions would have eliminated without any recurrence.

It is well-known that tobacco smoking is a significant risk factor for melanin formation and oral melanin pigmentation [8]. In addition, frequency and duration of smoking is directly related to the amount of oral pigmentation [39]. In the present systematic review, smokers were included in four studies, [21,28,30,33] and the recurrence rate of OPL in these studies was up to 40%. An explanation for this may be that the participants continued to smoke after SLT leading to the recurrence of pigmented lesions. Therefore it is highly advocated that patients with oral pigmentation should also be educated about the associated risk of smoking and occurrence of OPL. Patients should be discouraged from continuing smoking and health promotion efforts should be emphasized.

In 80% of studies [20–22,28,30–33] included, treatment for OPL using SLT (test group) was not compared to conventional surgical treatment strategy (control group). In the study by Hegde et al. [29] oral pigmented sites treated with surgical therapy showed significantly better outcomes as compared to Er:YAG laser treated sites at 6 months follow up. However, Ribeiro et al., [23] in a study of 6 months follow up showed comparable cosmetic outcomes for OPL treated with Nd:YAG lasers and conventional surgical therapy. The contrasting treatment outcomes in these studies [23,29] was attributed to the type of lasers and their absorption coefficient. Nd:YAG has a lower absorption coefficient in water and are preferentially absorbed in pigmented cells, causing effective degradation of these tissues [40]. By contrast, high water absorption and thin surface interaction with less tissue degeneration is associated with Er:YAG lasers [41]. Interestingly, with respect to the efficacy of individual laser types in management of OPL, only three studies [22,28,29] compared different types of lasers (CO2, Nd:YAG and Er:YAG), showing comparable outcomes among different laser types. The remaining 70% of the included studies [20,21,23,30–33] that showed lasers are effective in the treatment of OPL, did not include control groups in the form of different lasers. Therefore further RCTs comparing different laser types are recommended to ascertain the efficacy of multiple laser types in the management of OPL.

There is insufficient evidence to suggest that SLT is the first line of treatment in the management of OPL. Hence, further qualified RCTs with exclusion of smokers and presence of standardized control groups are needed to assess the efficacy of SLT in comparison to conventional treatment modalities in the management of OPL.

5. Conclusion

SLT is effective in the overall management of OPL including physiologic gingival pigmentation, smokers’ melanosis, and pigmentation in Laugier–Hunziker syndrome. Different laser types (CO2, Er:YAG and Diode) showed comparable outcomes in the treatment of OPL. However it is emphasized that related factors such as number of irradiation sessions and tobacco smoking are critical factors related to recurrence of pigmented lesions and therefore affect the success of SLT in their management. Therefore, it is recommended that further RCT with standard laser parameters and long follow up periods are warranted to study the outcomes of OPL with SLT.

Conflict of Interest Statement

The authors declare that they have no conflict of interest and all authors have read and approved the final draft.

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