The Effect of Photodynamic Therapy on Oral-Premalignant Lesions: A Systematic Review

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Abstract

Background: Dentists now have access to a wide range of unique treatment methods as a result of substantial scientific and technological breakthroughs in the field of dentistry. Photodynamic therapy (PDT) is a non-invasive treatment procedure that use photosensitizers, a specific wavelength of light, and the production of singlet oxygen and reactive oxygen species (ROS) to kill undesired eukaryotic cells (such as oral tumors) and harmful microbes. In several disciplines of dentistry, it is seen as a valid therapeutic option. The purpose of this study was to examine the effectiveness and side effects of PDT in the treatment of oral premalignant lesions.

Material and Methods: Three search engines (PubMed, ISI Web of Science, and the Cochrane Library) were used to conduct a systematic review using the phrases photodynamic therapy and PDT in combination with other terms. To define our study eligibility criteria, we used the Population, Intervention and Comparison, Outcomes, and Study design technique.

Results: Initial results were 33. Definitely, 18 studies met our selection criteria.

Conclusions: Our analysis suggests ALA-PDT as a promising therapeutic modality for OEL lesions which should be treated first with the topical ALA-PDT using either the LED or laser light for successful clinical outcome for OEL lesions.

Key words: Photodynamic Therapy, Photosensitizer, Aminolevulinic Acid (ALA), Methylene Blue (MB), Toluidine Blue, Oral Leukoplakia, Oral Erythroplakia, Oral Verrucous hyperplasia, Oral Lichen Planus.
Introduction
A variety of therapeutic approaches have been proposed for the treatment of oral per-malignant lesions (such as leukoplakia [OL], oral erythroplakia [OE], oral verru-uous hyperplasia [OVH] and oral lichen planus [OLP]). Some of the treatment options include topical medication (such as vitamin A, antibiotics, and steroids), LASER ablation, cryotherapy, and surgical excision. Non-surgi-cal treatment approaches for pre-malignant lesions (such as topical medication delivery) may be beneficial in the short term, but they have been linked to high recurrence rates. Furthermore, it has been demonstrated that surgical treatment of oral precancerous lesions increases mor-bidity and scar tissue development.

For the treatment of premalignant lesions in the mouth, photodynamic therapy (PDT) is a novel treatment option. PDT includes the interaction of a light source with a chemical dye or photosensitizer in the presence of oxygen (PS). As a result of this interaction, reactive oxygen species are formed, causing oxidative damage to microbial cell walls as well as pre-malignant and mal-liant cells. Oscar Raab discovered in 1900 that para-melia was destroyed by the interaction of acridine (a dye) and visible light in the presence of oxygen [32]. Later, Niels Finsen undertook research on the use of the arc light in phototherapy, for which he was awarded the Nobel Prize in 1903 [32]. Professor Hermann von Tappeiner, head of the Pharmacological Institute of the Ludwig-Maximilians University in Munich [33], coined the phrase ‘photodynamic action’ (‘photodynamische Wirkung’) in 1904. In 1913, the German physician Fried-trich Meyer-Betz conducted the first investigation with porphyrins, which was first dubbed photo radiation ther-apy (PRT). On his own skin, he evaluated the effects of hematoporphyrin-PRT. With early clinical argon dye LASER, John Toth, as product manager for Cooper Medical Devices Corp, Cooper Lasersonics, recognised the photodynamic chemical impact of the therapy and authored the first white paper renaming the therapy as Photodynamic Therapy (PDT). This was done to help fund the establishment of ten clinical locations in Japan, where the word radiation was associated with negative connotations [32]. The University of Berlin’s Auler and Banzer identified the characteristic red fluorescence of porphyrins in mouse tumours in 1942. This discovery marked the start of the field of photodynamic diagnost-ics (PDD).

PDT was used to treat 10 individuals with oral lichen planus (OLP) in a research by Rakesh et al. (1). The results demonstrated that OLP was completely eradicated, with no recurrence during a four-year follow-up period. Mirza reported similar findings. S et al. (17). According to the findings of these studies, PDT may be a potential therapy approach for the management of oral premalig-nant lesions (1-17). PDT treatment for oral premalignant lesions, however, resulted in recurrence and secondary infection in three individuals after six months, according to research (16). In this context, there appears to be consider-able disagreement over the effectiveness of PDT in the treatment of oral premalignant lesions. The goal of this study was to look at the efficacy and side effects of PDT in the treatment of oral premalignant lesions in a systematic way.

Material and Methods
-Focused Questions
1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were utili-sed to construct a focused query. The following was the question that was addressed: -
2. Is PDT useful in the treatment of premalignant lesions in the oral cavity?
3. Which are the photosensitizer most commonly used?
4. Is PDT cause any adverse effect during or post-treat-ment?
5. Follow-up and Recurrence Rate?
-Eligibility Criteria
The following requirements had to be met:
Original investigations, clinical studies, case reports, and intervention studies were all required. -the effica-cy of PDT in the treatment of oral premalignant lesions, and works written solely in English.
Review papers, experimental research, letters to the edi-tor, and unpublished works were not taken into account.

Search Strategy
In PubMed/Medline (National Library of Medicine, Bethesda, Maryland), Google Scholar, EMBASE, and the ISI Web of Knowledge database, the following keywords were searched from 2000 to 2020: Oral premalignant lesions, oral lichen planus, and photodynamic treatment are all conditions that can be treated using photodynamic therapy. The writers reviewed and double-checked the titles and abstracts of articles that satis-fied the qualifying requirements. The entire texts of eli-gible articles were checked and independently appraised using the title and abstract eligibility criteria. Following that, the authors discussed and agreed on the referen-ce lists of original and review studies that they thought were significant (Fig. 1). In the initial search, 33 studies were discovered. In total, 17 studies (1,2,4,5,8-13,15-17,23,24,26,28) were included and data was extracted from them. The current study’s design was tailored to primarily summarize the important data.

Results
-General characteristics of the studies
Pre-existing oral premalignant lesions with or without dysplasia that were clinically and histopathologically identified were included in all investigations (1,2,4,5,8-13,15-17,23,24,26,28). OL, OEL, OLP, and OVH were
Fig. 1: Flow chart shows study selection criteria based on Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.

seen in all premalignant lesions treated in all studies (1,2,4,5,8-13,15-17,23,24,26,28). 297 instances of premalignant lesions were documented in this study (1,2,4,5,8-13,15-17,23,24,26,28). The buccal and labial mucosa (maxilla and mandible), tongue, palate, floor of the mouth, bucco-gingival sulcus, and concomitant gingiva were characterized in fifteen investigations (1,4,5,8-13,15-17,23,24,26,28).

In a study by Koty Naik et al., the effectiveness of PDT was compared to that of conventional treatment (control group) in the management of premalignant lesions (12). (The OL and OLP acronyms stand for old and new and old In the research, PDT was compared to LLT and topical corticosteroids (17). Chuan et al. conducted a clinical evaluation of OLE and PDT utilising either light-emitting diode or laser light (26).

Discussion
In 2020, Dario et al. [10] treated 11 OL with PDT; the reported result revealed that 40% of the lesion had a complete response (CR), and 46.7% reported a partial response (PR), while in 13.4% no response (NR) at the end of the treatment and most commonly involved site was the adherent gingiva. In 2007, Chen et. al., treated 32 OL lesions with topical ALA with PDT; the reported results revealed that 1/3 of the 32 OL lesion could achieve a CR after treatment twice a week. Even after 10 months of treatment, 94 percent (16/17) of PR or NR OL lesions were challenging to attain a CR. During the follow-up period, 7.8% (28/36) of the follow-up OL lesions showed a small increase in the size of the residual lesion [8]. In 2006, Aghahosseini et al., reported 5 OLP lesion, treated with MB mediated PDT. Two lesions completely resolve (CR). A PR (more than 50% improvement) was observed in TWO other lesions. There was no recurrence in improved lesions after 9 months follow-up. But no improvement was observed in lesion on the tongue [16]. In study, Umber et al. (2014), lesion showed CR after 4 session of PDT and no recurrence was noted after 12 mon-
# Table 1: Characteristics of included studies based on Population, Intervention, Comparison and Outcome (PICO) model.

| S.NO | Author | Year of Publication | Lesion | Cases and Control | Photoactivator drug | Photoactivator light tool and protocol timing | Follow –up | Side effect |
|------|--------|---------------------|--------|-------------------|---------------------|---------------------------------------------|------------|------------|
| 1    | Aleksandar Sieron et al. (24) | 2003 | OL | 12 | 10% ALA | No. of session; - 6-8, Irradiated was performed in several sessions using light from an argon- pumped dye LASER at 635nm wavelength, delivering a total dose of 100j/cm² per session. 10-20% margin around lesions in the field of irradiation also included. The treatment time – 15min at low fluence rate & was interrupted periodically to prevent excessive photosensitizer bleaching | (1) One recurrence was observed during 6 months (2) Moderate pain during treatment, localized erythema and oedema were observed immediately after light exposure. (3) 30% patients had an acute pain (4) PDT associate with secondary infection in 3 patients |
| 2    | Soliman et al. (2) | 2005 | OLP | 25 | | Diode LASER is calibrated and measured to the desired power. The irradiated lesion area was selected by the aid of aiming pilot laser beam then was irradiated by 8-watt diode LASER. The lesion was irradiated until the area changed to white color i.e. photocoagulation was completed | 6 months | Recurrence that occurred after three months in 1 case and four months in 2 cases |
| 3    | Farzane Aghahosseini et al. (16) | 2006 | OLP | 2 | Methlene Blue(MB) | No. of session; - 3 (3,7,15 days) A diode LASER (632nm, CW) was used as light source. The lesion and 1cm of their surrounding marginal zone were illuminated with a spot size of 2.5 – 3cm². Large lesion were illuminated with multiple spots. A fluence of 100j/cm² was used. | 9 Month | No side effects |
| 4    | Chuan-Hang Yu et al. (8) | 2007 | OVH | 36 | 20% ALA | Irradiated with an LED red light at 635 +/- 5nm separated by five 3min rests for a total of 1000s (fluence rate, 100mW/cm², light exposure dose, 100j/cm²) 1.5 – 2h after topical application of 20%ALA onto oral lesions | No side effects |
| 5    | Chuan-hang Yu et al. (26) | 2009 | OEL | 46 | 20% ALA | No. of sessions: once a week till the lesion is completely gone. For a total of 1,000 seconds, the lesion was irradiated with either an LED red light at 635 +/- 5nm or a 635nm laser light (fluence rate, 100mW/cm²; light exposure dosage, 100j/cm²). The 1000-second treatment was split into five 3-minute sessions and one 100-second irradiation session separated by five 3-minute sessions. | During PDT, 35 OEL with severe throbbing pain or a burning sensation received light therapy under local anaesthetic with 2% lidocaine. |
Table 1 cont.: Characteristics of included studies based on Population, Intervention, Comparison and Outcome (PICO) model.

| No. | Author et al. (Year) | Year | Population | Intervention | Comparison | Outcome | Notes |
|-----|----------------------|------|------------|--------------|------------|---------|-------|
| 6   | Hung pin Lin et al. (15) | 2010 | Oral Ver- | 40% ALA | Both OVH & OEL lesions was irradiated with a 635nm LASER light generated by the Art-LASER Power-adjustable (from 0 to 1200nm) diode LASER. (Fluence rate-100nW/cm², light exposure dose, 100j/cm²). The 1000s-treatment period was divided into five 3-min rests. | Initially sever throbbing pain and marked burning sensation notice. |
| 7   | Gal Shafirstein et al. (11) | 2011 | OL | 23 | 5ALA | No. of session; -8 (separated by 6 to 8 week). A PDL that emits (pulsed dye LASER) light with a 585nm wavelength in pulses of 1-5ms at intervals of 1 to 3 sec. | 365 days Sensitivity, soreness, swelling, burning feeling, taste modification, and ulceration were among the minor side effects experienced after therapy. |
| 8   | Jaya Chandran et al. (23) | 2012 | OLP | 20 | 5% Methylene Blue | No. of session; -4 (1,4,7,15 day). Lesion with 1cm surrounding marginal zone was illuminated with xenon arch lamp light at wavelength of 632 +/- 5nm for 20 min. total dose delivered was 120j/cm² for each sitting. | 2nd & 4th week after therapy No side effects |
| 9   | Sigrid et al. (31) | 2013 | OLP | 14 cases | MAL-PDT | The light exposure was done three hours after the MAL cream was initially applied. Using a light-emitting diode (LED) light source, a radiant exposure of 75 J/cm² of red light in the range 600 to 660 nm was provided at irradiances of 100 to 130 mW/cm². Four high-power LEDs (Lumeon I Emitter, Lumileds, San Jose, CA) were used to deliver light via a 2-cm acrylic guide. | 30 months No side effect |
| 10  | Umberto Romeo et al. (5) | 2014 | OPVL | 1 | 20% Gel 5ALA | No. of session; - 4, Diode LASER used with 635nm wavelength. Each application consists of five 3 min and one 100s irradiations with five 3 minutes breaks for a total of 100s (fluence rate - 100mW/cm², total energy dose 100j/cm²) with fractionated protocol. | No side effects |
| 11  | Hsin Ming Chen et al. (4) | 2015 | OEL | 20 | 5ALA | No. of session; - once in a week for 6 months, irradiated with 635nm by LED light | No side effect |
| 12  | Kotya Naik et al. (12) | 2016 | OL & OLP | 21 | 98% 5ALA | No. of session-12, Irradiated by light emitting diode(LED) blue light with a wavelength of 480nm and intensity >500mW/cm² | Not mentioned No side effect |
| 13  | Shivani Sharma et al. (28) | 2017 | Erosive OLP | 1 | 5-ALA | No. of session; -1, Irradiated by red diode LASER 660nm. | 6 months No side effects |
| 14  | Sana Mirza et al. (17) | 2018 | Erosive-atrophic OLP | 15 | Toluidine Blue 50 μl topical application | No. of session; - 2(2 times weekly). Irradiation by GaAlAs LASER with wavelength of 630nm, 10mW/cm², continuous treatment, spot size; -1cm² | 1 year No side effects |
### Table 1 cont.-1: Characteristics of included studies based on Population, Intervention, Comparison and Outcome (PICO) model.

| Study | Year | Population | Intervention | Comparison | Outcome |
|-------|------|------------|--------------|------------|---------|
| Koty Naik *et al.* (2016) | 2016 | 24 OL lesions and 29 OLP lesions | Pulsed dye laser (PDT) | Topical corticosteroid | CR: 10 (83.33%), PR: 8 (66.66%), NR: 2 (16.66%) |
| Chen *et al.* (2007) | 2007 | 24 OVH lesions, 65 OL lesions and 6 OEL lesions | Topical ALA-PDT | | CR: 24 (100%), PR: 65 (100%), NR: 6 (100%) |
| Gallal Shafirstein *et al.* (2011) | 2011 | 23 patients of OL aged between 37 to 79 years | Topical ALA and pulsed dye laser | | PR: >75%, NR: <25% |
| Fatemeh *et al.* (2019) | 2019 | 11 patients of OLP lesion | Toluidine blue (Tol) PDT | Topical corticosteroid | CR: 11 (100%), PR: 10 (90.9%), NR: 1 (9.1%) |

Note: CR = Complete Response, PR = Partial Response, NR = No Response.
need to be continued for several weeks. Also, PDT can be used as an adjuvant therapy in combination with topical steroid for resistant or recurrent OLP [13]. Hung Pin et al. (2010) reported 40 OVH and 40 OEL treated with ALA-PDT, finding that all 40 OEL lesions displayed CR after an average of 3.6 PDT therapy, with 38 showing CR and 2 showing PR after an average of 3.4 PDT treatment [13]. In 2018, study Mirza Sana et al.; reported 25 OLP lesion on the tongue or buccal mucosa treated with toluidine blue PDT, LLLT and topical corticosteroids application, they indicated that PDT and LLLT both are effective in treatment of Erosive-atrophic form OLP. However, PDT showed superior results than LLLT, while corticosteroid application reduced significantly greater pain as compared to both PDT and LLLT groups [17]. In 2018 study, Rakesh et al.; treated 10 patient Erosive OLP between the age group of 20-70 with ALA-PDT, reported excellent result in 1 session with remarkable reduction in sign and symptoms, although post-inflammatory hyperpigmentation persisted and no recurrence in 4 year follow-up [1]. Similarly Shivani et al. (2017), treated Erosive OLP with ALA –PDT, showed excellent result in 1 session with no recurrence in 6 month follow-up [28]. Sadaksharam et al. (2012) reported 20 patients OLP treated with 5% Methylene Blue mediated PDT (xenon arc Lamp), noted that no improvement in 3 cases; moderate improvement in 9 cases; marked improvement in 6 cases and CR in two cases. Aleksander Sieron et al. (2003), reported a study, 12 patient with OL treated with 10%ALA using PDT (argon-pumped dye LASER). Out of 12 Patient, 10 showed CR, 2 – NR and 1 recurrence was observed during 6 months [24]. Yu-Chuan et al. (2009) investigated 46 OEL cases, 20 of which were treated with ALA-PDT using LED light and 26 of which were treated with ALA-PDT using LASER light of the same wavelength (635), and found that the 20 LED light-treated OEL lesions exhibited CR in 17 instances and PR in three cases. CR was found in 25 of the 26 laser-light-treated OELs, whereas PR was found in one [26]. Sigrid et al. (2013) described 14 instances of OLP where one side was treated with MAL-PDT and the other was not. All of the participants in the experiment had improved after three months. Two patients had relapsed by the 6-month follow-up, although new lesions were only found in areas where amalgam fillings were in direct contact. These patients were subsequently advised to have their fillings replaced, and as a consequence, the mucosa healed completely.

Conclusions

Our findings point to ALA-PDT as a viable treatment option for dysplastic OEL lesions, which should be treated initially with topical ALA-PDT using either LED or laser light for a positive clinical result. Furthermore, topical ALA-PDT is a minimally invasive approach that may be utilized to treat recurring or resistant lesions on a regular basis without creating major short- or long-term negative effects. However, because there is insufficient evidence to support ALA-PDT as a first-line treatment for dysplastic OEL lesions, more longitudinal follow-up studies should be encouraged to demonstrate its therapeutic usefulness in this area. In addition, more comparative studies should be conducted to compare the effectiveness of PDT with LED or laser therapy and with other therapeutic modalities for dysplastic OEL lesions.

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Conflict of interest
Non declared.