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A Review of the Surgical and Nonsurgical Treatment of Oral Leukoplakia

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Abstract

Objective: The aim of this paper was to assess the surgical and non-surgical treatment of Oral Leukoplakia (OL). Methods: The surgical, topical or systemic nonsurgical treatments or combination of both were reviewed. Several clinical trials have investigated the treatment of OL patients with the use of supplements.

Results: The intervention should be considered in accordance with the result of the biopsy. Various methods of treatment are discussed with different protocols. There is still no consensus; however, several methods are used in the management of patients with OL. Both surgical and non-surgical methods demonstrated great effectiveness in accordance with the degree of dysplasia.

Conclusions: At this time, randomized controlled trials for treatments of OL demonstrate no evidence of efficient treatment in preventing malignant transformation or recurrence. There is, indeed, the need of the establishment of a consensus on the treatment of OL to ensure approachable uniformity and comparable results.

Keywords: Oral leukoplakia; Potentially malignant disorder; Topical treatment; Surgical treatment

Abbreviations

OL: Oral Leukoplakia; N-: 4-Hydroxyphenyl; 4-HPR: Fenretinide; PDT: Photodynamic therapy; ALA: 5-Aminolevulinic Acid

Introduction

Oral Leukoplakia (OL) is a potentially malignant lesion described as white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer [1,2]. May coexist with varying grades of dysplasia and is generally considered a potentially malignant disorder. OL is therefore an excellent clinical model for examining the cancer prevention strategies [3].

Etiology of OL is not clearly established. Smoking, alcohol abuse, lasting mechanical injuries, Candida albicans infection and differences of local galvanic potentials are reported as the most important cause factors [4,5]. OL can accompany systemic disorders like hormonal disturbances, gastric juice secretion, diminished saliva secretion or iron deficiency anemia. It is also stated that EBV, HPV (16 and 18 types), HSV and HIV viruses significantly influence OL development and carcinogenic transformation [6]. As its etiology cannot be established, treatment is difficult and shows insufficient efficacy [7].

In order to conduct treatment for OL, the degree of epithelial dysplasia may be assessed. In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended [8]. However, OL presenting low to moderate malignant risk may be either completely removed or not, and the decision should consider other factors such as location, size and, in the case of smokers, the patient's engagement in smoking cessation [9-11]. OL surgical treatment may be performed either through conventional surgery [9,11,12], electro cauterization, laser ablation [13,14], or cryosurgery [15].

The purpose of this paper is to present a review of therapies for OL. The methodology was a search of the literature. A Medline search from 1971 to February 2016 was conducted using the following keywords: Oral Leukoplakia; potentially malignant disorder; Topical treatment; Surgical treatment. The primary outcomes of interest were clinical resolution, follow-up, and when reported, malignant transformation and recurrence of surgical and nonsurgical of OL.

Surgical treatment of oral leukoplakia

The standard treatments for OL range from careful consideration to complete resection [16,17]. However, OL presenting low to moderate malignant risk may be either completely removed. Surgical treatment for OL may prevent the development of oral squamous cell carcinoma, provided by assuring that the resection margins are adequately thick and free of epithelial abnormalities [17,18]. However, it has been shown that surgical intervention does not appear to prevent OL from developing recurrence [19]. Malignant transformation of these lesions is independent of drug or laser therapy [18,20].

Dysplasia severity is the most common risk factor associated with malignant transformation [21] however; Mogedas-Vegara et al. [22] could not demonstrate this fact in their study. Therefore, the use of CO_2 laser for the treatment of OL is a reliable, reproducible technique associated with a very low complications rate. No randomized trials are reported in the literature that compares surgery with CO_2 laser in terms of local recurrence and malignant transformation [23].

Curative surgical resection has the potential to be effective as a

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prophylactic treatment of lesions on the tongue having a tendency to develop cancer. Some studies have reported a higher frequency of malignant transformation in the case of untreated non-homogenous leukoplakia [24,25].

There is no significant association between the degree of epithelial dysplasia and the risk of recurrence of OL treated by surgical resection. This led to the suggestion that lesions with moderate to severe dysplasia can be effectively treated with surgical intervention [17]. In comparison with the data describes in the literature, the average is 7.7%-40% for recurrence of the lesion, and 0.83%-14% for malignant transformation [24-34].

Laser: The CO_2 laser has been recommended to treat benign oral lesions as well as premalignant lesions such as OL [35-37]. The treatment of OL using CO_2 laser can be best obtained by ablation or vaporization of the lesion. Ablation being done at defocused mode (achieved by moving the laser away from the tissue and beyond its focal length), reduces the power and depth of penetration of the laser beam (200-400 lm per pass), limiting the destruction to the epithelium and hence resulting in lesser pain, swelling and even scarring with better regain of elastic property of the tissue [38].

As an alternative, the CO_2 laser vaporization (λ=10.6 μm, continuous wave, defocused) is an established procedure that has been in use for more than 35 years [39-42]. This technique has been proven to be very effective, being associated with recurrence rates of less than 10% in 282 OL over 5-168 months [42].

Vaporization of tissue with a defocused laser beam is, however, not entirely minimally invasive. Horch et al. [40,41] have shown histologically that thermal laser energy carbonizes superficial parts of epithelium resulting in re-epithelization being delayed for more than two weeks and the possibility of healing with scarring. A delay in wound healing can also be an encumbrance for the patient.

The CO_2 laser treatment of potential lesions is most efficacious when used in defocused mode. It may be assumed that the heat generated can also destroy deeper-lying dysplastic cells [43].

As the use of a scalpel may induce wide areas of denudated mucosa with unfavorable scarring changes and secondary functional alterations as surgical sequelae; the use of CO_2, Nd:YAG, and KTP lasers has been suggested for vaporization or excision of OL [44], because their precision allows a conservative and site-specific, minimally invasive surgery with sterilization of the surgical area and minimal intraoperative hemorrhage. These lasers also permit a better postoperative period, with less swelling and pain and healing with minimal scarring [44-48]. Additional advantages of lasers include an optimal visualization of the surgical area, seal of lymphatic, and nerve endings which minimizes the chances for neoplastic cells seeding and the elimination of precancerous fields (dysplasia) neighboring the leukoplakia with minimal surgical morbidity. These particularities would justify investigations on their use for oral precancerous treatment [44-48].

Nonsurgical treatment of oral leukoplakia

No surgical intervention is chosen in cases where the lesions involve a large area of the oral mucosa, when patients present with high-risk medical problems for surgery, or when patients refuse surgical intervention and after follow-up without surgery [49,50]. In addition, few studies have reported the long-term outcomes of OL without surgery [51]. Drug intervention was considered as one of the non-surgical treatment options. Bleomycin, Retinoic acid (vitamin A), and carotenoids have shown to be unsuccessful in the treatment of OL; all of these offered little benefit and had strong side effects, thereby being unfit for continued use [51].

There is no effective therapy by nonsurgical means, as seen above; therefore, large numbers of leukoplakia patients have been surgically treated to date. Surgical resection is a feasible management option for patients with accessible and localized lesions and can prevent the cancer from spreading. Nevertheless, there is no denying that extensive resection is a feasible management option for patients with low-grade oral squamous carcinoma may be recognized as overtreatment. Several studies have suggested that surgery has a questionable value as a treatment strategy for all types of leukoplakia on the grounds that surgical intervention does not prevent oral potential malignant lesions from undergoing malignant transformation [52,53].

Kuribayashi et al. [54] reported that 74 of 237 lesions (31.2%) without surgical treatment were reduction or disappearance. The average amount of time from the patient's initial visit until lesion size reduction or complete disappearance was 42.1months. There is a possibility that removal of considerable irritation for a long time contributes to the treatment of this disease. Some OL resist treatment and exhibit local recurrence (up to 30%) [55]. These results demonstrated that some lesions of OL might reduce in size or disappear without surgical treatment during the long-term wait and see [54].

Carotenoids

Beta-Carotene: Carotenoids belong to a group of highly hydrophobic molecules with little or no solubility in water [56]. Beta-carotene is a precursor to vitamin A and [56-60] excessive consumption of beta-carotene causes a change in skin color, which becomes very yellowish, called carotenodermy [56]. The absence of side-effect is reported by Sankaranarayanan et al. [61] in patients treated with beta-catotene. The use of beta-carotene has been recommended for the prevention of potential malignant lesions, such as OL and cancer [61], possibly oral cancer. The potential benefits and protective effects against cancer are possibly related to its antioxidant action [62-65].

Liede et al. [62], claim that a diet supplemented with beta-carotene may prevent changes in the oral mucosa, especially in smokers who have low blood levels of vitamin C and beta-carotene, compared to non-smokers. It has also been shown that beta-carotene has a better therapeutic clinical response in preventing OL lesions in smokers than in nonsmokers. The patients received 30 mg of beta-carotene, 1000 mg of ascorbic acid, and 800 IU of alpha-tocopherol per day for nine months. The antioxidant supplementation significantly increased serum and tissue levels of beta-carotene, ascorbic acid, and alpha-tocopherol, but these changes did not correlate strongly with clinical improvement [63].

Sankaranarayanan et al. [61], showed that one third of patients (15 out of 46) who used 360 mg of betacarotene per week for 12 months presented complete resolution in OL. In sessions for assessment a

year after the treatment, eight out of the 15 (54%) of the patients who had a complete response presented recurrence.

In another study [66, 23] patients with OL were treated with beta-carotene, in oral doses of 90 mg / day for three cycles of three months each. Of the 18 patients who completed the study, 6 (33.3%) had a complete clinical response. No significant clinical signs of toxicity were detected in any of the patients 66.Garewal et al. [67] evaluated 50 patients with OL treated with beta-carotene at a dose of 60 mg / day for six months. Only two patients (4%) had a complete clinical response. Relapses were found in four patients. A second biopsy was obtained after six months of treatment in 23 patients. There was no change in the degree of dysplasia in 14, with improvement of at least one degree in nine (39%). In the studies with beta-carotene, the percentage of patients with clinical resolution ranged from 4% to 54% with treatment using dosages from 20 to 90 mg / day for periods of 3 to 12 months.

Retinoic acid (Vitamin A): Supplementation with retinoids for OL treatment begin in the 1960s, however, this treatment was not widely accepted due to its hypervitaminosis, teratogenic effects, side effects and toxicity [67,68]. Retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus through several proteins. Several processes are influenced by retinoids, such as production of keratin, the expression of growth factors and kinases, oncogenesis, apoptosis, production of collagen matrix, immune and inflammatory responses, cell differentiation, embryonic morphogenesis and carcinogenesis [56,58,59].

13-cRA retinoid is recommended for the treatment of OL and use of 13-cRA was shown to be more effective in solving OL [48,49]. However, the high rates of recurrence after short periods of interruption, together with their side effects are limiting factors [62,63,69].

Studies evaluating the therapeutic efficacy of vitamin A derivatives in the treatment of OL, resulted in satisfactory coefficients. In a study of 45 registered patients, seven (15.5%) were OL. Patients were given a fixed dose of 13-cRA (10mg / day) plus increasing doses (starting at 800 IU / day, up to 2000 IU / day) for four months. In this group of patients, 71% had complete clinical responses of OL [69].

A study carried out with retinoic supplementation (300,000 IU retinol acetate) to treat OL showed complete resolution in 52% of patients. The side effects observed included two patients who reported hypo salivation [60].

The supplementation with retinoic acid at various dosages for treatment of OL, 50% of patients had partial or complete clinical resolution of the lesions. In addition, for most patients with clinical resolution OL medication was discontinued. Some patients stopped retinoic acid treatment due to side effects. Moreover, during the evaluation of the topical use of 13-cRA (0.1% gel isotretinoin) for four months in patients with nine OL, 20% had a complete clinical response to treatment and no patients reported side effects [63,69,70].

Shah et al. [71] used 13-cRA in 16 patients with OL for six months. Three patients were treated with doses of 3 mg / day, eight to 5 mg / day, and five to 10 mg / day. Eleven patients completed the study: three had a complete clinical response (2 to 10 mg / day and 1 to 5 mg / day). Recurrence was observed in two out of three of these patients.

A study by Toma et al. [72] treated 16 OL subjects with 13-cis-retinoic acid, initially 0.2 mg / kg / day for three months and increasing by a further 0.2 mg / kg / day, in the following cycles of three months. The maximum dose was 1.0 mg / kg / day. Fourteen patients completed the trial and there was a complete response obtained at 0.4 mg / kg / day. After the treatment with retinoic acid has been discontinued, the patients were monitored for 12 months; two patients presented regression of the responses after six and nine months.

Studies on topical vitamin A and its derivatives in the treatment of OL were reviewed by Gorsky & Epstein [73]. The use of topical retinoic acid at 0.05% was evaluated in 26 patients with OL. Patients were monitored for 23 months. Ten patients that had a partial clinical response or none had pre and post-treatment biopsies, and the average degree of histological characteristics did not change. Twenty-seven percent of the patients had a complete clinical remission. The OL recurrence was observed in approximately 40% of the patients after its application, concluding that the topical use of vitamin A acid showed a limited effect in the treatment of OL [74].

In another study, the clinical efficacy of topical calcipotriol (vitamin D3 analog) was compared to retinoic acid in the treatment of hyperkeratotic oral lesions (leukoplakia) [75], 40 patients had histologically results OL. Twenty patients were treated with calcipotriol (50 mg / g), and 20 with tretinoin cream (0.05%). The treatment was five weeks and monitored for four months. The monitoring results showed complete resolution of OL in 16 patients in both groups.

In a 10-year study of patients with OL, Scardina et al. [76] reviewed the effectiveness of topical use of isotretinoin 0.18% compared to 0.05%. The concentrations of 0.18% and 0.05% were given to two different groups and given twice daily for three months. Clinical resolution was 85% in the 0.18% group, with no adverse reaction. In addition, epithelial dysplasia was gone and there was a significant reduction in the lesion size. In systemic use at dose 300 thousand IU of retinoic acid (vitamin A), a clinical resolution of 50% was showed. In topical use with a dosage range from 0.05% to 1% was obtained a clinical resolution of 10% to 27%.

Lycopene: Lycopene is another nonsurgical treatment for OL. It appears to be a very promising antioxidant as a treatment modality in OL and can protect cells against damage and play a protective role against progression of dysplasia by inhibiting tumor cell proliferation and the first report of efficacy of lycopene against human oral cancer cell was published describing the significant therapeutic effect [77].

Nagao et al. [78] tried to investigate the association between serum micronutrient levels and OL. The serum levels of lycopene among men with OL were significantly lower than those of controls. And Gupta et al. [79] tried to estimate the relation between nutrient intake and prevalence of OL. They observed that tomato consumption the main source of lycopene has the most protective effect on OL among all dietary factors. To date, only one study evaluated the efficacy of lycopene in the clinical resolution of OL.

Lycopene is effective in the treatment of OL and it has been reported that a daily dose of 8 mg of lycopene was more effective than 4mg a day. This efficacy of lycopene was associated with its antioxidant properties [80].

Zakrzewska [81] concluded that lycopene brings about histological changes of a significant degree in patients with OL.

Fenretinide: The compound N- (4-hydroxyphenyl) retinamide, also known as fenretinide (4-HPR) was synthesized in the United States in 1960 and is used for treating OL. This compound, similar to the vitamin A, is used for the chemo preventive treatment of various diseases, and has been studied and tested in clinical trials for the treatment of OL [82-84].

According to Tradati et al. [85] eight patients diagnosed with OL were treated with 4-HPR, by topical application twice a day for 30 days. The results showed, after one month of therapy, complete remission in two patients with OL, the others had a response higher than 75%, besides no side effects or distant sites were observed.

Therefore, given the side effects and counter-indications of antioxidizing agents, with the exception of lycopene, the use of agents requires careful control.

Photodynamic therapy: Photodynamic therapy (PDT) is a non-invasive method for the treatment of potential malignant lesions and cancers of the head and neck region [86,87]. The principle of PDT occurs through photochemical reactions associated with photosensitizing drugs which are photosensitizers, oxygen and visible light. After a period photosensitizer that accumulates in target tissue activated by exposure to low energy visible light with a specific wavelength for the drug.

The light source is consisted mainly by a portable laser diode and the light penetrates into the lesion, or by fiber laser transmission. This treatment through the application of the laser wavelength promotes activation of cell destruction by a radical oxidation process. Thus, PDT is a photochemical reaction, and photosensitizing agents are inherent, low systemic toxicity, the repair is especially true for regeneration instead of healing, important structures are maintained and preserved with good functional and aesthetic results [88,89].

Several photosensitizers have been developed: 1) photofrin has been approved in many countries for the treatment of esophageal cancer and lung cancer; 2) 5-Aminolevulinic Acid (ALA) has also been approved in several countries for the treatment of skin cancer; 3) Verteporfin for the treatment of macular degeneration 4) Foscan photosensitizer is the only one approved for the treatment of squamous cell carcinoma of the head and neck in Europe in 2001 [89].

In most of the cases of head and neck surgeries, the photosensitizer is given systemically by intravenous injection. ALA can be given topically for superficial extensive skin lesions or potential malignant lesions of the oral mucosa.

Zakrzewska et al. [90] reported three forms of treatment for 10 cases of proliferative verrucous leukoplakia; surgery, and carbon dioxide laser PDT. The PDT was given to five patients there was no relapse in three, although a white hyperkeratinisation halo was observed around the area subjected to the treatment in these patients. The results showed a rate of recurrence after surgical excision treatment (100% and 85.7%) for laser vaporization. Already PDT showed a better prognosis compared to other forms of treatment.

In the study of Kübler et al. [91], 20 OL were treated with PDT using ALA topical 20%, followed application of light at 630 nm, 100 W / cm2 and 100 J / cm2. After three months, five patients responded completely to treatment (there were no clinical signs of OL), four partially responded (the injury was reduced), three did not respond (no clinical change) and 1 had a partial response being subjected to a further treatment, which resulted in the disappearance of the lesion. No recurrence was observed in nine months after this treatment.

In another study, Sieron et al. [92] reported 5 OL treated with ALA topical 10% over the lesion followed by argon laser (635 nm 100-250 J / cm2). Four of the five patients responded completely. In one case, there was a recurrence after six months, however, after two additional sessions, the lesions disappeared completely. The author observed the therapeutic response to PDT OL in 12 patients treated topically with 10% ALA, activated by a laser at 635 nm and 100 J / cm2 per session for six to eight sessions. There was a complete response (total washing out of leukoplakia on visual inspection confirmed by biopsy specimen) in 10 cases (83%). A recurrence was reported after six months of control.

According to Chen et al. [93], 24 patients presenting OL used 20% of ALA-PDT, once a week; additional 24 patients used 20% of ALA-PDT twice a week. In the last group, eight responded completely to treatment, 16 partially and nine did not respond. All patients in the group twice a week responded significantly better than those treated only once a week. From studies using PDT, topical ALA in concentrations of 10 to 20% can be observed clinical resolution OL in 25% to 80% of cases.

Cryotherapy: Cryotherapy is a method that locally destroys lesional tissues by freezing in situ [92]. It has several advantages including bloodless treatment, a very low incidence of secondary infections, and a relative lack of scarring and pain [91-93]. Cryotherapy can be carried out with either a closed or an open system [94-104]. Closed-system cryotherapy offers a greater degree of temperature control but requires complex, delicate, and expensive equipment [94-100]. It is performed by direct contact of the cryoprobe onto the lesional surface. Because of the small and flat contact area of the cryoprobe end, closed-system cryotherapy is usually suitable for treatment of uniform, smooth-surfaced oral lesions less than 1 cm in diameter [93-99]. Open-system cryotherapy involves directly applying the cryogen to the lesion with a cotton swab [90,91] or a portable spray apparatus [94,102-104]. It is more difficult to maintain a constant lower temperature in the lesional tissues during the whole treatment period. However, it does not need expensive equipment. Open-system cryotherapy with the spray apparatus is suitable for treatment of medium and large oral lesions with either a smooth or a rough surface [94,102-104].

Closed-system cryotherapy has been used for treatment of OL lesions with promising clinical outcomes [93-99]. Sako et al. [96] treated OL lesions in 60 patients using a special cryosurgical unit, and all OL lesions showed complete regression after one to five treatments. Chapin and Burkes [97] used cryotherapy with a gold

cryoprobe to treat four patients with dysplastic and non dysplastic OL lesions and observed complete regression of all lesions after one or two treatments. Leopard [98] used closed-system cryotherapy with two consecutive freeze thaw cycles of up to 1.5 minutes to treat over 40 OL lesions in a 3-year period; only two extensive and long-term OL lesions failed to respond. Bekke and Baart [102] used cryotherapy with a cryoprobe to treat 35 OL lesions in 24 patients; all lesions showed complete regression after one to four treatments.

Al-Drouby [100] used cryotherapy with a cryoprobe to treat 30 OL lesions in 30 patients; 23 had complete removal, six had partial removal, and there was no response in one patient. Kawczyk-Krupka et al. [101] used cryotherapy with a contact scapular probe to treat 37 patients with OL; a complete response was obtained in 33 patients (89.2%) and recurrence was observed in nine patients (24.3%).

Open-system cryotherapy for OL is carried out by the direct application of either carbon dioxide snow or liquid nitrogen to OL lesions by the cotton swab or open spray [92-94,102-104].

Cryogun cryotherapy seems more efficient than cotton-swab cryotherapy to treat OL lesions, because the former needs approximately half of the treatment number to achieve complete regression of nearly equal-sized OL lesions compared with the latter. In fact, the cotton swab carries only a small amount of liquid nitrogen that cannot maintain a constant low temperature in the treated lesional tissues [92-94,102-104].

Miller 99 used a single liquid nitrogen spray for 45-60 seconds to treat OL lesions on the hard palate, soft palate, and buccal mucosa; all OL lesions were successfully eliminated after treatment. Goode & Spooner [103] used liquid nitrogen spray to treat OL lesions in 20 patients and observed complete regression of all OL lesions after one to four treatments.

Gongloff & Gage [104] used liquid nitrogen spray of two consecutive freeze thaw cycles to treat seven OL lesions; complete regression of all OL lesions was achieved after a single treatment. The results of the aforementioned studies indicate that either closed-system or open-system cryotherapy is very effective for the treatment of OL lesions.

Conclusion

Several clinical trials have investigated the treatment of OL patients with the use of supplements. The intervention should be considered in accordance with the result of the biopsy. However, OL presenting low to moderate malignant risk may be either completely removed or not, and the decision should consider other factors such as location and size. Both surgical and nonsurgical methods demonstrated great effectiveness in accordance with the degree of dysplasia. Surgical treatment of OL may be performed through conventional surgery. The causative agent of OL must be abandoned so that the follow-up treatment is successful. Although the administration of retinoic acid and beta-carotene has some efficacy to resolve OL. Given the side effects and counter-indications of antioxidizing agents, with the exception of lycopene, the use of agents requires careful control. At this time, randomized controlled trials for treatments of OL demonstrate no evidence of efficient treatment in preventing malignant transformation and recurrence. It is recommending close lifelong follow-up with new biopsies when changes are detected. It is necessary to strengthen further clinical trials to determine the effectiveness of treatment for the patient according to their follow-up, which allows us to differentiate successfully between surgical cases and observation.

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