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Management of Oral Leukoplakia – Non-Surgical and Surgical Treatment

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Abstract

Aim: To evaluate the efficacy of topical retinoic acid (A-RET gel-0.025%) in homogenous leukoplakia and diode laser in non-homogenous leukoplakia patients (speckled, nodular and verrucous). **Study Design:** Study included total 30 patients of clinically diagnosed cases of leukoplakia; homogenous leukoplakia (n = 15) and non-homogenous leukoplakia (n = 15). **Material and Method:** Homogenous leukoplakia patients were given treatment of topical A-RET gel and antioxidant, while non homogenous leukoplakia patients were surgically treated by diode laser. Patients were followed up for healing after diode laser. **Results**: Total regression was reported in almost all cases of homogenous leukoplakia within one month, without any recurrence. Speckled leukoplakia and buccal mucosa showed faster healing as compared to other types of non-homogenous leukoplakia with laser. **Conclusion:** A-RET gel and diode laser gives excellent results in homogenous and non homogenous leukoplakia cases respectively. Type of leukoplakia and lesion site plays an important role in prognosis of the lesion.

Keywords: Antioxidant, Diode Laser, Oral Leukoplakia, Tretinoin

1. Introduction

Oral Leukoplakia (OLK) is the most frequent Oral Potentially Malignant Disorder (OPMD)[1]. The malignant transformation rate ranges from 0.13% to 34%, for homogenous leukoplakia (1-7%) and speckled and verrucous leukoplakia (18-37%)[2].

Various treatment modalities for OLK have been proposed with varied success rates. Non-surgical treatment such as vitamin A analogues (retinoids) and other antioxidant vitamins and nutrients (i.e. beta carotene, vitamins C and E), bleomycin and curcumin can be considered as a good choice in homogenic OLK without dysplasia[1,3]. Vitamin A and related compounds (retinoids and carotenoids) were first attempted 30 years ago and there have been a significant number of studies on the use of retinoids[4]. Lycopene appears to be a very promising antioxidant as a treatment modality in oral leukoplakia and can protect cells against damage[3]. Surgical modalities include conventional scalpel surgery, electro coagulation, cryosurgery and laser surgery[3]. In among various surgical treatments laser techniques have helped improve surgical approaches and ultimate control of leukoplakia. Laser is the latest and advanced revolution in surgical field. Light has been used as a therapeutic agent for many centuries and this use of light for various therapies is referred to as phototherapy. LASER (Light Amplification by Stimulated Emission of Radiation) used as diagnostics and as therapeutics in the medical field from surgery to non-invasive processes. The basic principle involved in laser action is quantum nature of light and stimulated emission. Lasers produce heat that converts electromagnetic energy into thermal energy. Emitted laser has three characteristic features: Monochromatic, coherent and collimated. Lasers in oral medicine used are CO_2 laser, Nd:YAG, Ho:YAG, Er:YAG, Argon and Diode. CO_2 Laser is most commonly used in soft tissue surgeries[5].

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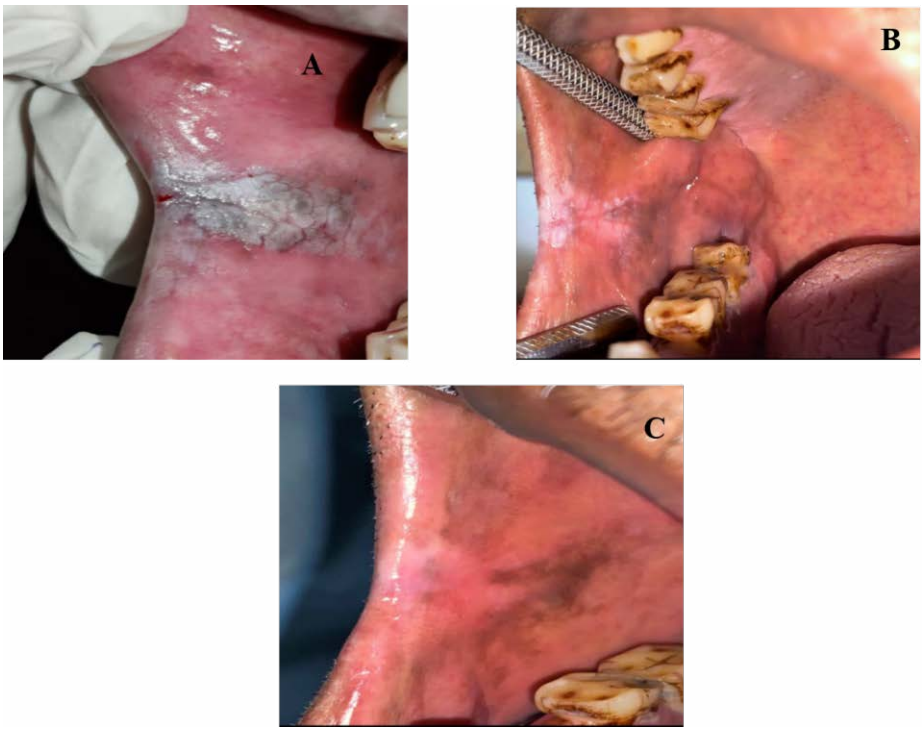


Figure 1. **A)** Depicts homogenous leukoplakia on right buccal mucosa; **B)** Regression of homogenous leukoplakia after 2 weeks on application of topical A-RET gel; **C)** Total regression of lesion after 4 weeks.

Diode laser is very commonly used in many surgical procedures and has many advantages such as reduced scar formation, less pain and bleeding and reduced chances of infection. Many researchers have also found that diode laser can be used to eliminate benign, potentially malignant disorders of the oral soft tissues[2,6]. The first successful operation of a diode laser was reported by several research groups in 1962[7]. Diode laser has become very popular in dentistry due to its small size and ease of use for minor soft tissue surgery. Based on its photothermal effect, it is used for the removal of small lesions of the oral mucosa by excision or vaporization procedures[8]. It is a semiconductor that uses solid-state elements to change electrical energy into light energy. The light energy from the diode laser with a specific wave length (810-980 nm) is greatly absorbed by the soft tissues than the hard tissues (teeth and bones), so diode lasers are preferred for the management of oral soft tissue lesions. Also this wavelength is absorbed by other chromophores, such as melanin and in particular, oxyhaemoglobin providing good haemostasis and effective cutting of tissue. Depth of penetration ranges from 2 to 3 mm into tissue, depending on wavelength. The laser light is coupled into a delivery fiber (typical fiber diameter: 200–400 mm) and either the delivery fiber itself or the laser light is coupled into fiber tips, both typically are used in contact mode[8,9]. All types of laser cause protein denaturation of keratinocytes in superficial epithelium, but diode laser destroys the underlying connective tissue along with the epithelium[9–11]. Recently lasers have also been tried as a treatment modality for OPMD and amazing results were proved[12].

The study is aimed to know the efficacy of A-RET gel in homogenous and diode laser in non-homogenous leukoplakia (speckled, nodular and verrucous).

2. Materials and Methods

The present study was conducted at Oral Medicine and Radiology Department, during the period of 2020 to 2021. Study protocol was approved by the Institutional Ethical Committee (IEC GDCH/OMR.14/2021). The study included 30 patients of oral leukoplakia which included 15 homogenous and 15 non-homogenous leukoplakia diagnosed on the basis of clinical criteria as mentioned below. On basis of history and data findings patients with bleeding, dyscrasia, chronic renal/liver disease, malignancy or metastatic lesion and major cardiac illness

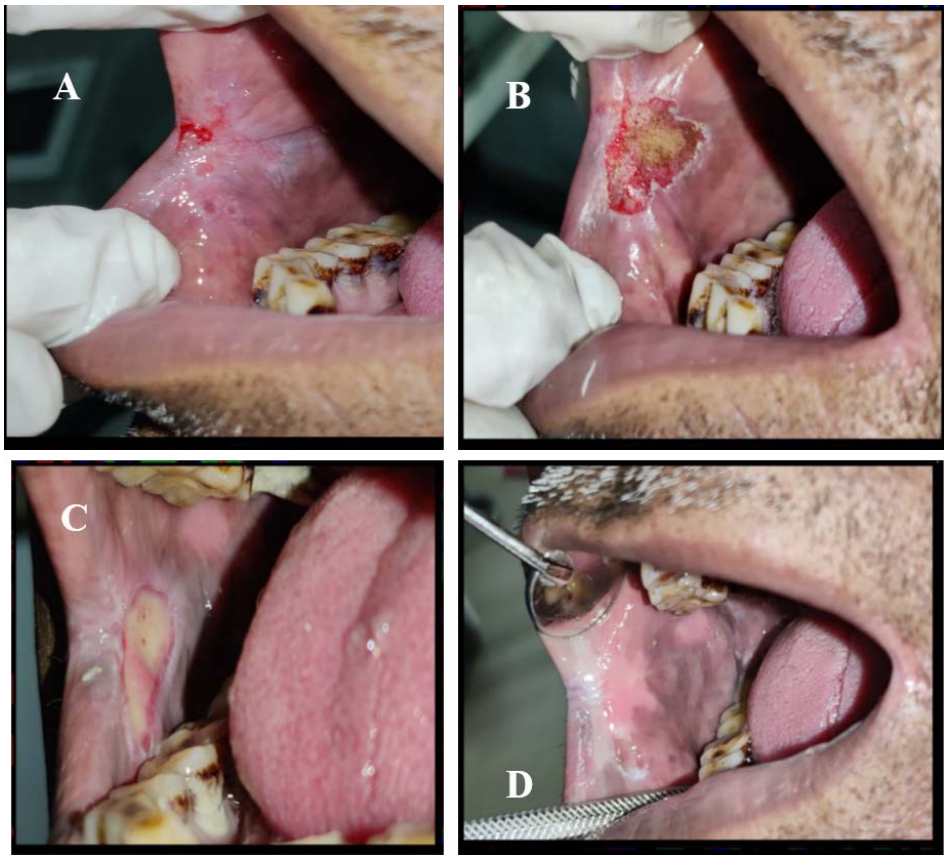


Figure 2. **A)** Depicts speckled leukoplakia on right buccal mucosa; **B)** Immediate post operative site after diode laser ablation; **C)** Site in healing stage after 1 week; **D)** Completely healed site after 4 weeks.

were excluded from the study. Pregnant patients were also excluded from the study. All demographic details, chief complaints, complaints regarding lesions, medical history and detailed tobacco habit history were recorded in all patients. Before doing laser surgery, all non-homogenous leukoplakia patients were assessed for diabetes mellitus and routine blood investigations were advised in all patients. In local examination of leukoplakia site, size, extension, colour, overlying mucosa and its texture, surrounding mucosa and pigmentation were recorded.

Homogenous leukoplakia patients were treated by topical therapy of retinoic acid (A-RET gel-0.025%) and antioxidant (Lycopene). Follow up was done every week for one month period and lesion size, colour and recurrence were noted. Scoring based on size of the lesion was assessed to predict the prognosis. (Score 1 - Total regression - Excellent, Score 2 - from any size to <1 cm- Good, Score 3-2-4 cm to <2 cm – Fair, Score 4- >4 cm to 2-4 cm - Poor). Incisional biopsy was taken in all non-homogenous leukoplakia cases and were graded according to criteria given by WHO 2005 epithelial dysplasia. All non-homogenous leukoplakia patients were treated by Starlas 100 diode laser (980 nm, 2.5-3-watt, continuous mode, contact mode) machine with laser tips of 300-400 µm diameter. Follow up was done on first day and at every week for 4 weeks. Postoperative complications, such as pain, bleeding, swelling as well as recurrence were evaluated. Pain was evaluated using VAS scale. Bleeding was evaluated as 0 - no bleeding, 1 - mild bleeding, 2 - moderate bleeding, 3 - severe bleeding. Swelling was evaluated by comparing with normal anatomic site for asymmetry. Score was given based duration of healing. (Score 1 - Healing within 1 week, Score 2 - Healing within 7-10 days, Score 3 - Healing within 11-20 days, Score 4 - Healing within 21-30 days, Score 5 - Recurrence)

2.1 Clinical Criteria[13]

Homogenous leukoplakia: Buccal mucosa and tongue most common involved sites having keratotic uniform white plaque like lesion with fissured, wrinkled or smooth overlying surface (figure 1).

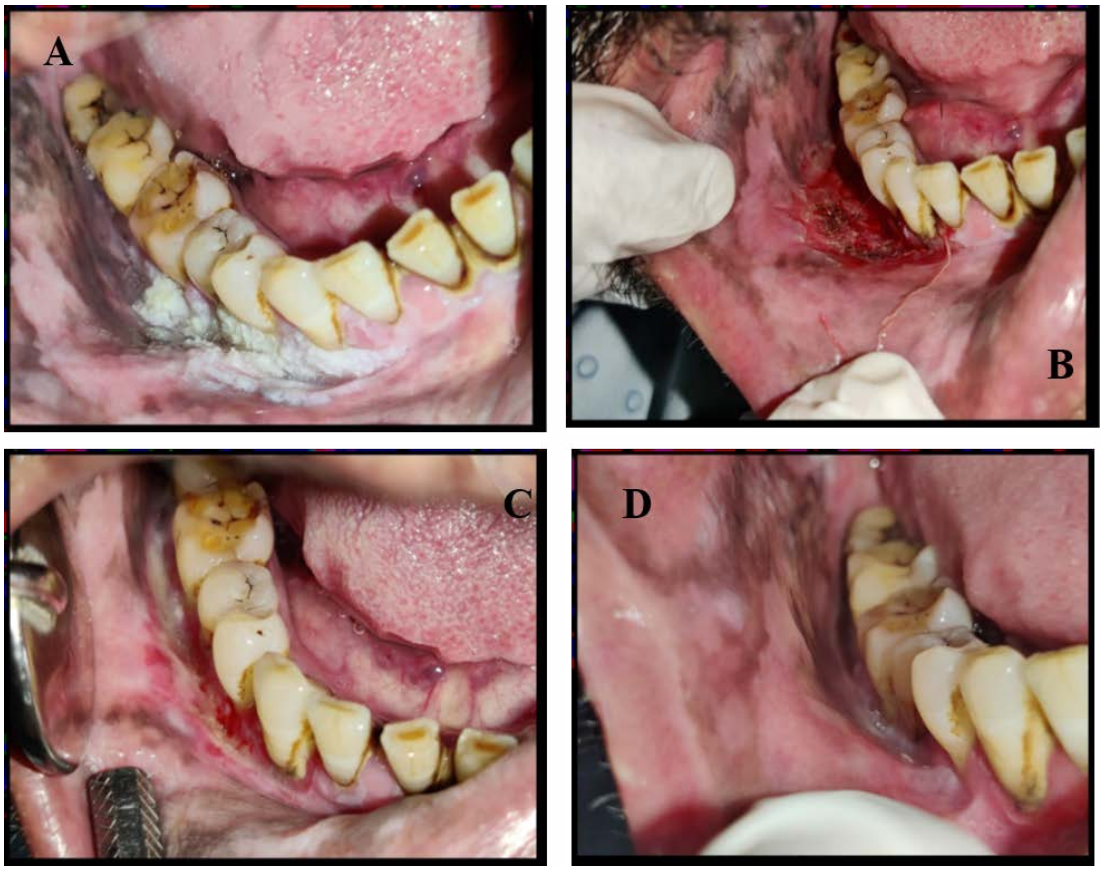


Figure 3. **A)** Depicts nodular leukoplakia on right lower buccal depth of vestibule; **B)** Immediate post operative site after diode laser ablation; **C)** Site in healing stage after 1 week; **D)** Completely healed site after 4 weeks.

Table 1. Demographic details of patients included in the study groups

	Homogenous leukoplakia (n = 15)	**Non homogenous leukoplakia (n = 15)**			Total (n = 30)
		Speckled leukoplakia (n = 05) (16.7%)	Verrucous leukoplakia (n = 07) (23.3%)	Nodular leukoplakia (n = 03) (10%)	
Gender					
Male	15(100%)	05(100%)	06(85.7%)	03(100%)	29
Female	00	00	01(14.3%)	00	01
Chi square value	3.399				
Significance	0.334(NS)				
31-40	02(13.3%)	01(20%)	03(42.9%)	02(66.7%)	08(26.7%)
41-50	08(53.3%)	01(20%)	00	00	09(30%)
51-60	03(20%)	01(20%)	04(57.14%)	01(33.3%)	09(30%)
61-70	02(13.3%)	00	00	00	02(6.7%)
71-80	00	02(40%)	00	00	02(6.7%)
Chi square value	23.857				
Significance	**0.021(S)**				

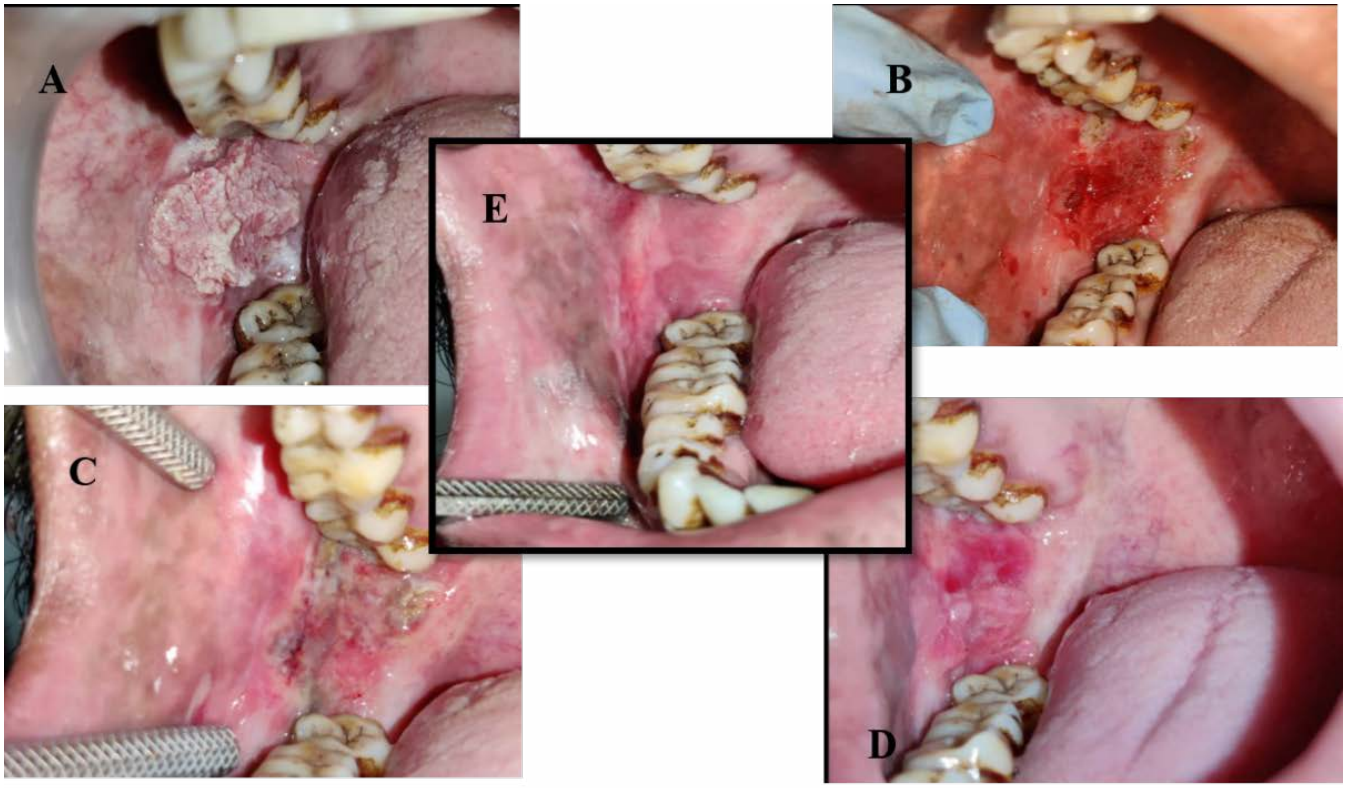


Figure 4. **A)** Depicts verrucous leukoplakia on right lower buccal depth of vestibule; **B)** Immediate post operative site after diode laser ablation; **C)** Site in healing stage after 1 week; **D)** Recurrence after 4 weeks; **s** Completely healed site after second diode laser on 2 months.

Non homogenous leukoplakia: Speckled leukoplakia - Buccal mucosa most common involved site having mixed red and white colour and plaque type of lesion with rough overlying surface (figure 2).

Verrucous leukoplakia: Buccal mucosa, attached gingival and depth of vestibule most common involved sites having white to mixed red and white colour thick fissured, papillomatous, proliferative or corrugated surface like appearance (figure 3).

Nodular leukoplakia: Buccal mucosa, lateral border of tongue, depth of vestibule and palate most common involved sites having white colour and thick condensed type of plaque or small polypoid outgrowths, rounded red or white excrescences (figure 4).

2.2 Statistical Analysis

The data was collected, coded and fed in SPSS (IBM version 23) for statistical analysis. The descriptive statistics included frequency and percentages. The inferential statistics included Chi square test for comparing categorial data. The level of significance was set at 0.05 at 95% confidence interval.

3. Results

Present study reported all male patients except only one female patient in verrucous leukoplakia group. Most common (86.7%) age group reported is 31-60 years. Smoking habit was found to be most common (56.6%) habit followed by combined smoking and smokeless habit. All the cases of homogenous leukoplakia were asymptomatic except one, whereas all patients of non-homogenous leukoplakia were symptomatic. Buccal mucosa was found to be the most common site involved in both homogenous and non homogenous leukoplakia. 86.7% of homogenous leukoplakia patients showed total regression within one month of duration with no recurrence. Speckled leukoplakia showed faster healing after diode laser ablation in non-homogenous leukoplakia. In two patients of verrucous leukoplakia recurrence was reported after diode laser ablation (Table 1-6).

Table 2. Distribution according to symptomatic and asymptomatic patients

	Homogenous leukoplakia (n = 15)	Non homogenous leukoplakia (n = 15)			Total (n = 30)
		Speckled leukoplakia (n = 05)	Verrucous leukoplakia (n = 07)	Nodular leukoplakia (n = 03)	
Symptomatic	01(6.7%)	05(100%)	07(100%)	03(100%)	16(53.3%)
Asymptomatic	14(93.3%)	00	0	0	14(46.7%)
Chi square value	26.250				
Significance	**0.000 (HS)**				
Findings	**Distribution of findings**				
Burning sensation	01(6.7%)	05(100%)	01(14.3%)	00	07(23.3%)
Growth	0	0	06(85.7%)	01(33.3%)	07(23.3%)
White plaque	15(100%)	05(100%)	07(100%)	03(100%)	30(100%)
Red erosive areas	0	05(100%)	0	0	05(16.7%)

4. Discussion

It is an accepted fact that it is indeed a challenge to the clinician to treat Oral Leukoplakia (OL). It is a potentially malignant lesion with high recurrence capacity and different methods both- medical and surgical are employed for its management[2],

In present study most common age group found was 31-60 years. Similar findings were also reported by other studies[6,12,14–16] (Table 1). Homogenous leukoplakia was found more in 41-50 years of age group and all cases were asymptomatic as they all visited dental OPD for some other dental reason (Table 2). Only one case reported with burning sensation as it was associated with Oral Submucous Fibrosis (OSMF). This shows most of the patients of homogenous leukoplakia are unaware of the lesion. Speckled, nodular and verrucous leukoplakia were found in 71-80, 31-40 and 51-60 years respectively. Non homogenous leukoplakia patients were symptomatic and presented with burning sensation, red and white lesion or growth. In speckled leukoplakia thinning of epithelial layer occurs especially in red area. Verrucous (VL) and nodular leukoplakia patients had complaint of growth and white patch respectively. The same findings were reported by other studies showing burning sensation in lesions with red component (speckled leukoplakia)[17,18]. In present study all 29 cases were reported in male whereas only one case of verrucous leukoplakia was reported in female patient having smokeless tobacco habit only (Figure 1). In Indian population using tobacco in the form of smoke is notably more in males than in females. Also co-worker influence and travelling are other possible explanations for male predominance. Previous studies in Indian population, support this analysis in our study[19,20].

The present study reported 56.7% cases of leukoplakia having smoking habit only, whereas 10% cases of leukoplakia having smokeless tobacco and 33.3% cases with combined habit (Table 3). The recent Global Adult Tobacco Survey in 2010 reported that 35% of the Indian adults are addicted to tobacco products, of whom 21% are chewers, 9% are smokers and the remaining 5% consume both supplements[21]. In homogenous leukoplakia 86.7% of patients had smoking habit and only two patients (13.3%) had combined habit explaining the presence of OSMF and Tobacco Quid Lesion (TQL) in two patients. Smoking is considered as one of the most common etiologic factors for leukoplakia[1,18]. Similar results were found in various studies[17]. VL may occur either in smoking or smokeless tobacco habit. In present study 3 cases of VL were noted only because of smokeless tobacco habit and were associated with OSMF and TQL. This suggests VL might be developed from smokeless tobacco related lesions. Not a single case of VL was reported with only smoking tobacco habit. Smokeless tobacco is also considered as one of the etiologic factors for OLK. Other rare factors such as Human Papilloma Virus (HPV) especially in case of

Table 3. Habit distribution among study group patients

Habits	Homogenous leukoplakia	Non homogenous leukoplakia		
		Speckled leukoplakia	Verrucous leukoplakia	Nodular leukoplakia
Smoking alone	13(43.3%)	3(10%)	0(0)	1(3.3%)
Smokeless alone	0(0)	0(0)	3(10%)	0(0)
Smokeless+ smoking	2(6.7%)	2(6.7%)	4(13.3%)	2(6.7%)
Chi square value	20.561			
Significance	**0.002((HS)**			

Table 4. Site wise distribution of study group patients

Sites					
	Homogenous leukoplakia (n = 15)	**Non-homogenous leukoplakia** (n = 15)			Total (n = 30)
		Speckled leukoplakia (n = 05)	Verrucous leukoplakia (n = 07)	Nodular leukoplakia (n = 03)	
Buccal mucosa	13(86.7%)	05(100%)	04(57.14%)	01(33.3%)	23(76.7%)
Lower buccal depth of vestibule	0	0	02(28.6%)	01(33.3%)	03(10%)
Dorsal/Lateral surface of tongue	02(13.3%)	0	0	0	02(6.7%)
Gingiva	0	0	01(14.29%)	0	01(3.3%)
Palate	0	0	0	01(33.3%)	01(3.3%)
Chi square value	21.967				
Significance	**0.038(S)**				

Proliferative Verrucous Leukoplakia (PVL) or genetic also can be present. Smoker's palate was found in all patients except in smokeless tobacco habit associated verrucous leukoplakia. The aetiology is probably related more to the high temperature rather than the chemical composition of the smoke, although there is a synergistic effect of the two. Hypermelanosis was found in all patients. Nicotine appears to directly stimulate melanocytes to produce more melanosomes, which results in basilar melanosis with varying amounts of melanin incontinence[22].

Buccal mucosa was found to be the most common site (76.7%) involved in present study (Table 4). The buccal mucosa carries highest propensity towards leukoplakic involvement. Exposure of this region of oral mucosa to higher amount of toxic metabolites, derived from tobacco, suspended in saliva is possibly responsible for its pathogenesis. The most common sites are the buccal mucosa, alveolar mucosa and lower lip. The topography of the buccal mucosal involvement also differs with the modality of tobacco consumption: Such as the leukoplakic patch commonly affects the posterior part of the buccal mucosa in patients using smokeless tobacco, but the smokers are rather prone to be affected with a buccal patch that is situated more anteriorly[1,11,16]. Present study supports this statement as two cases of combined smoking-smokeless tobacco habit associated verrucous leukoplakia were reported on posterior buccal mucosa. In present study malignant potential found to be increasing from nodular leukoplakia, speckled leukoplakia and verrucous leukoplakia. Speckled leukoplakia lesion having ca in situ was associated with severe stage of OSMF associated with combined smoking and smokeless habits suggesting role of combined habit and other habit related lesions. VL from buccal mucosa might be converted from pre-existing leukoedema or leukoplakia. Three cases of VL associated with only smokeless tobacco habit were

Table 5. Homogenous leukoplakia follow up (n = 15)

	1st visit	1st week	2nd week	3rd week	4th week
Burning sensation	01	01	0	0	0
Hypermelanosis	15	15	15	15	15
Lesion size					
<1 cm	0	0	07(46.7%)	03(20%)	0
<2 cm	10(66.7%)	10(66.7%)	04(26.7%)	04(26.7%)	0
2-4 cm	03(20%)	03(20%)	02(13.3%)	02(13.3%)	01(6.7%)
>4 cm	02(13.3%)	02(13.3%)	02(13.3%)	01(6.7%)	01(6.7%)
Total regression	0	0	0	05(33.3%)	13(86.7%)
Recurrence	0				

Table 6. Laser follow up for healing period in non homogenous leukoplakia

Healing period	Speckled leukoplakia (n = 05)	Verrucous leukoplakia (n = 07)	Nodular leukoplakia (n = 03)
<7 days	0	0	0
7-10 days	01(20%)	0	0
11-20 days	04(80%)	03(42.9%)	01(33.3%)
21-30 days	0	02(28.6%)	02(66.7%)
Recurrence	0	02(28.6%)	0
Chi square value	8.464		
Significance	0.206(NS)		

found on gingiva and lower buccal depth of vestibule. VL was found to be having more severe dysplasia followed by moderate dysplasia. One case of nodular leukoplakia was found on hard palate having smoking habit. When leukoplakia occurs on hard palate, it usually takes thick plaque condensed appearance of nodular leukoplakia due to its keratinized mucosa. Similar results reported in the studies on Indian population[6,10,21,23]. Some studies also reported most common site tongue followed by gingiva and buccal mucosa[17,24].

Excellent results were obtained in all cases of homogenous leukoplakia treated by topical retinoic acid (A-RET gel-0.025%) and antioxidant (Lycopene). Out of 15 cases, 100% results were obtained in lesion size of <2 cm and 66.7% in 2-4 cm and 50% in lesions with >4 cm within 4 weeks. Hypermelanosis was not regressed in any cases (Table 5). No recurrence were noted. Various studies found excellent results using topical tretinoin. They compared lesion colour or treatment duration but not the size of lesion[4,25]. A-RET gel and lycopene proved to be the drug of choice in homogenous leukoplakia.

Non homogenous leukoplakia patients were treated by diode laser. Follow up was done on 1st post op day, 1st week, 2nd week and after four weeks. Post operative bleeding, pain, swelling, burning sensation, lesion colour and recurrence were noted. Except pain and swelling for one week in patients with OSMF due to constant trauma over operated site was reported in speckled and verrucous leukoplakia, no other complaints reported (Table 6). Similar results reported by many studies[6,11,15,26]. Only fewer studies are available in the present literature regarding usage of diode laser in the management of potentially malignant disorders. It has many advantages over traditional scalpel excision[6,17]. Exceptionally precise tissue ablation at low power settings, diode lasers is neither absorbed too much nor too little in water and haemoglobin, enabling precise char free soft tissue ablation and hemostasis[27], Minimal postoperative pain and edema in a laser surgery is due to its effect on nerve endings; reduced the thermal damage to surrounding tissue and sealing of small lymphatic vessels[2]. Speckled leukoplakia showed faster healing followed by nodular and verrucous leukoplakia. All speckled leukoplakia were present on

anterior buccal mucosa whereas all verrucous leukoplakia were present on middle or posterior buccal mucosa, gingiva or in vestibular depth. Nodular leukoplakia also was found to be present on either posterior buccal mucosa or vestibular depth or on palate. This shows significance of clinical type of leukoplakia as well as site involvement. Thus, anterior buccal mucosa provides better and faster healing. This can be due to chances of trauma from occlusion are more in posterior buccal mucosa and also inability to maintain proper hygiene[12].

Recurrence was noticed only in two cases of verrucous leukoplakia after a month. One patient was having moderate stage of OSMF with lesion on posterior buccal mucosa and severe dysplasia histologically. Another patient was female patient with gingival location and ca in situ histologically. The highest risk of malignant transformation is appeared to be with proliferative verrucous leukoplakia[17]. Gingiva also carries highest risk of malignant transformation[28]. Studies showing no recurrence after 6 months follow-up were recorded[2,11]. The depth of penetration is more with diode laser thus it completely ablates the epithelium owing to minimal chance of recurrence[10]. Lasers causes sealing of lymphatic and nerve endings which minimizes the chances for neoplastic cells seeding and the elimination of precancerous fields (dysplasia) neighbouring the leukoplakia with minimal surgical morbidity[3,27,29]. Histopathological features reported from studies carried out for wound healing post laser treatment show few myofibroblasts, suggesting to be effector of wound contraction[30]. Present study also reported excellent wound healing in all patients.

5. Conclusion

Topical A-RET gel along with antioxidant provides excellent results in homogenous leukoplakia without any recurrences. Diode laser provides excellent results in non-homogenous leukoplakia. Speckled leukoplakia has least healing period as compared to nodular and verrucous leukoplakia. Buccal mucosa has highest satisfactory results as compared to vestibular depth and gingiva.

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