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EFFICACY OF 5% TOPICAL IMIQUIMOD IN ORAL LEUKOPLAKIA

Dentistry

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ABSTRACT

Introduction: Oral leukoplakia, a common potentially malignant disorder of the oral mucosa, carries a significant risk of malignant transformation. Treatment options include both surgical and non-surgical approaches. Imiquimod, an immune response modifier, has shown promise as a non-invasive treatment for oral leukoplakia. To evaluate the efficacy of 5% topical Imiquimod in the treatment of oral leukoplakia and assess clinical and histological outcomes. **Material and method:** This randomized clinical study involved 39 patients with histopathologically confirmed oral leukoplakia. Patients advised to apply topical 5% Imiquimod three times per week for 6 weeks in homogeneous and non-homogeneous leukoplakia. Clinical responses were measured by changes in lesion size, color, and surface alterations, while histological evaluation was performed using the Van der Waals Oral Leukoplakia Staging system before as well as after treatment. Statistical analysis was performed using the Chi-square test, with a p-value <0.05 considered significant. **Results:** The study showed a statistically significant reduction in lesion size, keratinization, and dysplasia in both homogeneous and non-homogeneous leukoplakia. Buccal mucosa demonstrated the highest response to treatment. Side effects were minimal and well tolerated. **Conclusion:** Topical 5% Imiquimod is an effective non-invasive treatment for oral leukoplakia, particularly for non-homogeneous types. It offers a promising alternative to surgical intervention, reducing morbidity associated with invasive procedures.

KEYWORDS

Dysplasia, Imiquimod, PMD- Potentially malignant disorder, oral leukoplakia

INTRODUCTION:

Cancer reminds us of the fragility of existence, urging us to cherish every moment and relationship. Oral cancer is the most common type of cancer of head and neck, with annual worldwide incidence in excess of 300,000 cases.[1,2] The disease is an important cause of death and morbidity, with a 5-year survival of less than 50%.[1] In India, 20/100,000 population are affected by oral cancer, which accounts for around 30% of all types of cancer. Most of the oral cancer are associated with habit and are preceded by asymptomatic clinical lesion collectively referred to as oral potentially malignant disorder (OPMD).[2] OPMDs includes Oral leukoplakia (OLP), erythroplakia, reverse smokers' palate, erosive lichen planus, oral submucous fibrosis (OSMF), lupus erythematosus and actinic keratosis. [2-4] The term "leukoplakia" was first applied by Schwimmer in 1877, who first used the term to describe a white patch of the oral mucosa.[5,6] Oral leukoplakia is one among important OPMD of the oral mucosa.[3-5]

It is considered to be multifactorial origin of the lesion. Smoking, alcohol abuse, lasting mechanical injuries, Candida albicans infection and differences of local trauma or galvanic potentials are reported as the most important causative factors. It is also stated that EBV, HPV (16 and 18 types), HSV and HIV viruses significantly influence OLP development and carcinogenic transformation of this lesion.[5,6-8] Oral leukoplakia has a comprehensive global review point at a prevalence of 1.5%-4.1% and malignancy conversion rate ranging from 0.1% to 36.4%.[6,7] Prevalence of leukoplakia in the age-group of 51-60 years and males are most affected. OLP is commonly present in buccal mucosa (76%), alveolar sulcus (19%), and tongue (5%).[8]

Two main clinical types of OLP are recognized, being homogeneous and non-homogeneous leukoplakia. The distinction of these is purely clinical, based on surface colour and morphological (thickness) characteristics, and do have some bearing on the outcome or prognosis. [3,7] A diagnosis of OLP is made when a predominantly white lesion at clinical examination cannot be clearly diagnosed as any other disease or disorder of the oral mucosa and in this situation a tissue biopsy from the lesion site proves to be very valuable.[5]

The treatment of oral leukoplakia involves eliminating the causative factor, most commonly tobacco use, which may result in lesion regression. When no cause is identified, or if the lesion persists, other therapeutic approaches are necessary. These include surgical excision, cryosurgery, CO2 laser ablation, and non-surgical treatments such as carotenoids (β-carotene, lycopene), vitamins [L-ascorbic acid (vitamin C), α-tocopherol (vitamin E), retinoic acid (vitamin A), and fenretinide], and bleomycin, which have been explored. Finding new therapeutic agents that can prevent the progression of precancerous lesions to cancer or even induce their regression remains a significant challenge. Imiquimod, a synthetic small molecule belonging to the imidazoquinolinamines family, has shown promise. Each gram of its 5% cream formulation contains 50 mg of imiquimod in an off-white, oil-in-water vanishing cream base. It is an immune response modifier with potent antiviral and antitumor properties, mediated through Toll-like receptors (TLR7 and TLR8).[1,4,9,10] Imiquimod 5% cream topically has proven to be an effective treatment for external genital warts, superficial basal cell carcinoma, herpes labialis, actinic keratosis and OLP.[9,10] The purpose of the present study is to evaluate curative response of 5% Topical Imiquimod in the treatment of oral leukoplakia.

MATERIAL AND METHOD:

This randomized clinical study was approved by the Institutional Ethical Committee (IEC/GDCH/OMR.15/2022). All ethical guidelines were followed, and written informed consent was obtained from the patients selected for the study. The study was conducted in the Department of Oral Medicine and Radiology. A total of 39 patients with oral leukoplakia caused by tobacco use in the form of smoking, smokeless tobacco, or a combination of both, irrespective of age and gender, were included in the study. Patients with comorbid conditions or major illnesses, pregnant women, individuals allergic to the drug, lactating mothers, and patients with other habit-related lesions such as Oral Submucous Fibrosis (OSMF), Tobacco Quid Lesion (TQL), or Oral Squamous Cell Carcinoma (OSCC) were excluded from the study.

All patients were subjected to detail case history and thorough clinical examination. All universal precautions were followed on clinical examination. All required data were recorded in the proforma. The cases of oral leukoplakia were confirmed by history, clinical examination, and histopathological examination performed by incisional biopsy of the lesion at the baseline visit. After biopsy, patients without dysplasia excluded from the study.

All included patients received Topical 5% Imiquimod (Glenmark

Pharmaceuticals India Pvt Ltd.) mixed with benzocaine gel, applied three times per week (in-office) for 2 weeks, followed by three times per week at home on alternate days for 30 minutes over the next 4 weeks. The treatment lasted for 6 weeks, with follow-up visits scheduled weekly. Patients were recalled every week for 6 weeks after the start of treatment. The outcome was assessed clinically every 2 weeks (at the 2nd, 4th, and 6th weeks) and histologically at the end of 6 weeks.

Clinical response was measured by evaluating the size of the lesions, color changes, surface alterations, and decreased pigmentation. The Van der Waals Oral Leukoplakia Staging (OLEP) system was used to quantify both clinical and histological changes pre- and post-treatment. For lesions that did not resolve clinically, an additional three applications were given over a 2-week period. Patients were monitored for adverse effects through direct questioning and clinical examination at each visit. The efficacy parameters were analyzed to determine any statistically significant changes from baseline to the end of the 6-week period. Qualitative data were analyzed using the Chi-square test, and a p-value of less than 0.05 was considered statistically significant.

RESULT:

The study enrolled 39 patients with homogeneous and non-homogeneous leukoplakia, all of whom were treated with topical 5% Imiquimod. The mean age of the participants was 51.42 ± 12.02 years, and the buccal mucosa, followed by the commissure, was the most commonly affected site (Table 1). Smoking (bidi/cigarette) was the most common habit, followed by the use of smokeless tobacco and alcohol.

All patients were treated for 6 weeks, and the time-wise therapeutic response for homogeneous and non-homogeneous leukoplakia was compared at baseline, the 2nd week, 4th week, and 6th week. Statistical analysis revealed a highly significant p-value of <0.001 (Figure 1A, B and 2A, B). After the 2nd, 4th, and 6th weeks of treatment, both homogeneous and non-homogeneous leukoplakia showed a reduction in keratinization, evidenced by a decrease in lesion size. Changes in color from white or red and white to nearly normal mucosa were also observed. Surface changes, including the transition from wrinkled, plaque-like, ulcerative, or nodular forms to nearly normal mucosa, were noted, which were statistically significant (p-value <0.001). A reduction in pigmentation was also observed, though this was not statistically significant (Tables 2 and 3). Histological improvements, as evaluated by Van der Waals staging, were noted before and after treatment in both homogeneous and non-homogeneous leukoplakia, which was statistically highly significant (p-value <0.001) (Table 4).

Table 1: Table shows of mean age of patient, Distribution of patients according to types of leukoplakia and involvement of site

Mean Age (yrs)	51.42 ± 12.02
Type of leukoplakia n(%)	
Homogenous	17(43.58)
Non-homogenous	22(56.42)
Site of lesion n(%)	
Buccal mucosa	39(100)
Commissure	32(82.05)
Labial mucosa	6(15.38)
Palatal mucosa	10(25.64)
Alveolar mucosa	3(7.69)
vestibule	7(17.94)

Table 2. Comparison of therapeutic response of clinical parameters in homogeneous leukoplakia at different time intervals

Clinical parameters	At Baseline n (%)	At 2 weeks n (%)	At 4 weeks n (%)	At 6 weeks n (%)	P Value
Size					
1-2 cm	-	-	3 (20)	8 (66.66)	<0.001**
2-4 cm	4 (23.52)	5 (29.41)	9 (60)	4 (33.33)	
> 4 cm	13 (76.47)	12 (70.58)	3 (20)	-	
Total	17 (100)	17 (100)	15 (100)	12 (100)	
Colour					
White/gray	17 (100)	17 (100)	10(66.66)	2(16.66)	<0.001**
Red and white	-	-	-	-	
Near to normal mucosa	-	-	5 (33.33)	10 (83.33)	
Total	17 (100)	17 (100)	15 (100)	12(100)	
Clinical Pattern					
Plaque like	17 (100)	15 (88.23)	2 (13.33)	-	<0.001**
Wrinkled/furrowed	-	2 (11.76)	8 (53.33)	5 (41.66)	
Ulcerative	-	-	-	-	
Near to normal mucosa	-	-	5 (33.34)	7 (58.33)	
Total	17 (100)	17 (100)	15 (100)	12 (100)	
Pigmentation					
Present	15 (88.23)	15 (88.23)	12 (80)	10 (83.33)	0.92
Absent	2 (11.76)	2 (11.67)	3 (20)	2 (16.66)	
Total	17(100)	17 (100)	15 (100)	12 (100)	

Table 3. Comparison of therapeutic response of clinical parameters in non-homogeneous leukoplakia at different time intervals

Clinical parameters	At Baseline n (%)	At 2 weeks n (%)	At 4 weeks n (%)	At 6 weeks n (%)	P Value
Size					
1-2 cm	-	1 (4.55)	8 (38.09)	13 (92.85)	<0.001**
2-4 cm	7 (31.81)	8 (36.36)	11 (52.38)	1 (7.14)	
> 4 cm	15 (68.18)	13(59.09)	2 (9.52)	-	
Total	22 (100)	22 (100)	21 (100)	14 (100)	
Colour					
White	-	-	17 (80.95)	2 (14.28)	<0.001**
Red and white	22(100)	22 (100)	2 (9.52)	-	
Near to normal mucosa	-	-	2 (9.52)	12 (85.72)	
Total	22(100)	22 (100)	21 (100)	14 (100)	
Clinical pattern					
Plaque like	-	-	12 (57.14)	3 (21.42)	<0.001**
Wrinkled/ furrowed	-	-	4 (19.04)	-	
Ulcerative	21 (95.45)	21(95.45)	2 (9.52)	-	
Nodular	1 (4.55)	1 (4.55)	-	-	
Near to normal mucosa	-	-	3 (14.28)	11 (78.58)	
Total	22 (100)	22 (100)	21 (100)	14 (100)	
Pigmentation					
Present	18 (81.81)	17(77.27)	12 (57.14)	9 (64.28)	0.32
Absent	4 (18.19)	5 (22.73)	9 (42.86)	5 (35.71)	
Total	22(100)	22 (100)	21 (100)	14 (100)	

Table 4. Van der Waal staging at baseline (At baseline) and at 6th week (After treatment) in homogeneous and non-homogeneous leukoplakia

Stage	At Baseline n (%)	At 6 weeks n (%)	P Value
Homogeneous leukoplakia			
Stage I	-	6 (60)	<0.001**
Stage II	-	4 (40)	
Stage III	4 (23.52)	-	
Stage IV	13 (76.47)	-	
Non homogeneous leukoplakia			
Stage I	-	11 (91.66)	<0.001**
Stage II	-	1 (8.33)	
Stage III	7 (31.82)	-	
Stage IV	15 (68.18)	-	

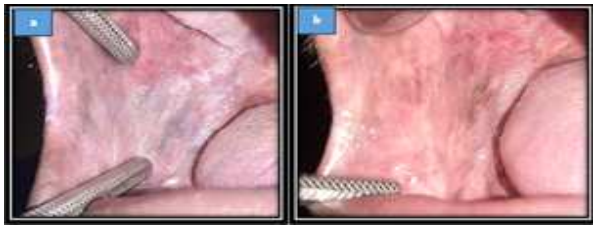

Figure 1A: (a) Intraoral Photographs Showing Homogenous Leukoplakia Present on Right Buccal Mucosa Before Treatment {Van der Wall-Stage IV}, (b) After 6 Weeks of Treatment (5% Imiquimod) {Van der Wall-Stage I}

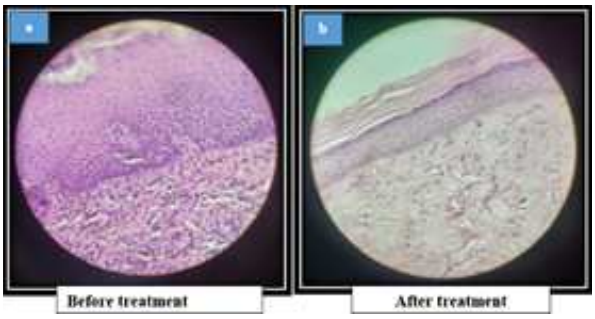

Figure 1B: Microphotograph Showing Regression of Dysplasia from Moderate (a) to Mild After (b) 6 Weeks of Treatment(H&EX400)

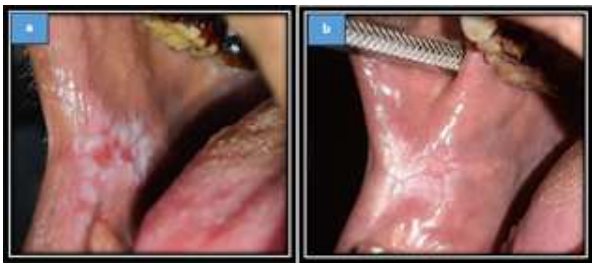

Figure 2A: Intraoral Photograph Showing Non-Homogenous Leukoplakia Present on Right Buccal Mucosa (a) Before Treatment {Van der Wall-Stage IV}, (b) After 6 Weeks of Treatment (5% Imiquimod) {Van der Wall-Stage I}

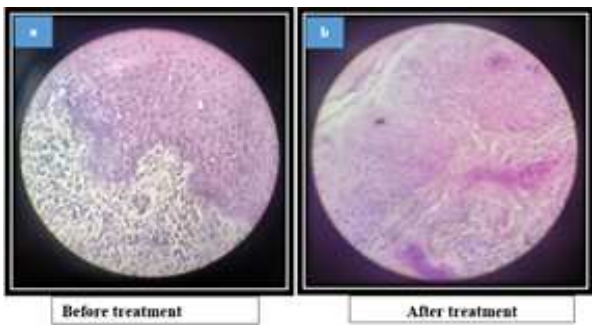

Figure 2B: Microphotograph Showing Mild Dysplasia Before Treatment (a) and Mild Dysplasia After 6 Weeks of Treatment (b) (H&EX400)

DISCUSSION:

Oral leukoplakia is an important potentially malignant disorder of the oral mucosa.[8] The concept of identifying oral lesions with a precancerous nature referring to a pathological process with an increased risk of future malignant transformation is to prevent the development of full-blown malignancy in the affected area. Over the past decade, there has been ongoing discussion about how best to treat oral leukoplakia. Various treatment modalities, both medicinal and surgical, have been employed in its management. The present study aimed to evaluate the clinical features, etiological factors, and therapeutic responses to 5% Topical Imiquimod in patients with oral leukoplakia.

The mean age for present study was 51.42 ± 12.02 years and male to female ratio was 38:1. The habit of tobacco smoking and smokeless form was far less prevalent in females than in males and the impact to the male patients was observed. Tobacco use was more prevalent among men in the older group, lower wealth status and education, manual occupation, separated/ divorced/ widowed, alcohol consumers, residents of rural area and north east region and less access to information.[11] Males are the working gender and money earner among the Indian subcontinent. Tobacco smoked and chewed for various reasons as it acts as stress reliever and increases the arousal level physiologically.[12] Yang SW et al.[13], Ashwini K et al.[14], Venkat A.et al[15] and Kusiak A et al.[16] shows the male predominance in their studies similar to present study.

Tobacco usage is the most important known etiological factor in the development of oral leukoplakia, but other factors such as nutritional deficiency, fungal etiology, Epsteinbar virus and genetic susceptibility are also involved in the etiopathogenesis of OLP.[5,7] In the present study, all patients had a tobacco habit, either in the form of smoking or smokeless products, such as bidi, cigarettes, gutkha, pan masala, and snuff. The habit of smoking bidi was the most common, recorded in 31 (79.48%) patients, followed by a combination of bidi and cigarette smoking in 7 (17.94%) patients, and cigarette smoking alone in 1 (2.56%) patient. Smoking habits showed cytomorphological changes, including an increase in nuclear diameter (ND) and a reduction in cellular diameter (CD). The increase in nuclear size could be attributed to an inflammatory response caused by chronic irritation of the oral mucosa from tobacco use. The results of a study conducted by Bánóczy[17] showed that the permeability of leukoplakic tissue to the tobacco carcinogen nitrosonornicotine was higher than that of normal buccal mucosa. This increased mucosal permeability in smokers seems to support this finding. The hyperplastic and hyperkeratotic epithelial changes seen in leukoplakia lesions represent a protective reaction of the tissue.[17,18,19] The oral mucosa, constantly irritated by tobacco use, may turn over more rapidly and become more permeable to carcinogens. This irritation is likely caused by the chemical components of tobacco, which may directly stimulate the epithelial keratinocytes or activate cells in the connective tissue. Interestingly, less differentiated cell types were observed, leading to oral epithelial dysplasia.[18,20,21]

Clinical morphology of oral leukoplakia can be classified as homogeneous leukoplakia and non-homogeneous leukoplakia based on the texture, color, thickness, and regularity of the lesion.[7,13] In present study, out of 39 patients of leukoplakia, 17(43.58%) patients had homogeneous leukoplakia and 22(56.42%) patients had non-homogeneous leukoplakia. Ulcerative surface was common in speckled type, while homogeneous type showing plaque like/furrowed or wrinkled appearance. All homogeneous type of lesion were white in colour while non-homogeneous type shows mixed red and white pattern. In present study 2 patients of non-homogenous leukoplakia had complaint of burning sensation. All patients of homogenous leukoplakia were asymptomatic. Progression from homogenous leukoplakia to non-homogenous leukoplakia transforms from keratotic to non-keratotic explaining absence of complaint in homogenous leukoplakia patients. In speckled leukoplakia thinning of epithelial layer occurs especially in red area.[22,23]Buccal mucosa (100%) was found to be the most common site involved in present study followed by commissure (82.05%) in both homogeneous and non-homogeneous type of leukoplakia. The same findings were reported by other studies Deliverska EG et al.[7], Yang SW et al.[13], Mohammed Abidullah et al.[23] and Parlatescu I et al.[24] and showing burning sensation in lesions with red component (speckled leukoplakia).[22,23] Hypermelanosis(Pigmentation) was found in 32 (82.05%) patients. Nicotine appears to directly stimulate melanocytes to produce more melanosomes, which results in basilar melanosis with varying amounts of melanin incontinence.[25]

Based on clinical and histological findings staging of oral leukoplakia was given according to Van der Waal staging before treatment in homogeneous and non- homogeneous leukoplakia and Stage III and stage IV was commonly found in present study. Similar result noted studies conducted by Mane et al.[4], Prashanth Shetty et al.[18], Adam Michcik et al.[21], Brouns et al.[26], Rubert A et al.[27] and Singh M et al.[28]. Leukoplakia is characteristically asymptomatic, but infrequently the patient may complain from pain, burning sensation and discomfort. Although, the lesion may be discovered during routine oral examination or in some instances, the patient may seek professional consultation as the lesion enlarges and becomes more obvious or changed in color. The early lesion is usually nonpalpable macule, later, particularly in longstanding or persistent form of leukoplakia the surface may become rough and raised, thus becoming speckled or verrucous type, this clinical difference in appearance of the lesion may represent stages of malignant transformation or may associated with high risk of malignant transformation.[27,29]

All patients were kept on 6 weeks follow up in present study. All clinical forms of leukoplakia responded to 5% Topical Imiquimod cream. After 2nd week, 4th week as well as 6th week of treatment homogeneous as well as non-homogeneous shows decreased in

keratinization in terms of decreases in size of lesion. Change in colour from white and red and white to near to normal mucosa noted. Surface changes also seen from wrinkled, plaque like, ulcerative or nodular form to near to normal mucosa. (Figure 1A,B and 2A,B) Which is statistically significant (p- value- <0.001). At the end of 6th week still some patients showed partial regression of leukoplakia, so as to increase the response of lesion to 5% topical Imiquimod the duration can be increased up to 9 week or 12 week and number of applications can also increase up to 5 times a week. As Alhadlaq et al.[30], J.P. Allam et al.[31], Antonio M.et al.[32] and Özbağçıvan et al.[33] and increased time duration in their study ranging from 9 weeks to 12 weeks to get the desirable result.

Therapeutic histological evaluation after 6th week showed response in all types of leukoplakia (homogeneous and non-homogeneous). In the present study, post treatment biopsy all 22 patients (homogeneous and non-homogeneous leukoplakia) given staging as per Van der Wall. There was decrease in dysplasia seen from baseline to the end of 6th week was seen statistically highly significant (p value- 0.003). Mane et al.[4] and Alhadlaq et al.[30] shows the similar findings like present study. Imiquimod acts on the innate and the adaptive immune responses both directly and indirectly[34-36]. Imiquimod decreases keratinization by inducing apoptosis in keratinocyte cell line and decreases dysplasia by reducing effect of the pro-survival protein Bcl-2, and transfection of Bcl-2 into tumour cells blunts Imiquimod's pro-apoptotic effects, and thus achieve antitumor action.[9,10,22-25] These effects of Imiquimod lead to decrease in size of OLP clinically and dysplasia histologically (homogeneous and non-homogeneous), which results in changes in stage of OLP from stage III and stage IV to stage I and stage II.

The use of Imiquimod in leukoplakia has been reported by very few studies till date. As with all drug, side effects may occur when using Imiquimod and severity of effect is dose dependent. Most common side effects are application site reaction, such as etching, burning, bleeding, pain, stinging, tenderness, irritation and induration. Other side effects include upper respiratory tract infection, sinusitis and headache.[4,9,31,32,37] None of our patients reported any local or systemic adverse reactions during treatment and also after the cessation of drug application.

Limitation And Future Prospect:

Present study included small sample size, larger sample size along with systemic conditions with various mixed lesion caused by smoking/nonsmoking tobacco along with leukoplakia should be considered. In the present study there was no equal distribution of sample in age and gender, type of OLP, and staging of OLP, which may vary the result. Long treatment duration and hesitation for post treatment biopsy led to loss of follow up of patients. Further studies are needed for the optimal dosing and long- term outcomes of Imiquimod treatment for dysplasia management. The result of the current research suggests that 5% Topical Imiquimod could be used as a reliable non-invasive therapeutic modality to treat oral leukoplakia.

CONCLUSION:

Squamous cell carcinoma prevention in premalignant lesions is achieved through Imiquimod's ability to activate the immune system, inducing apoptosis in dysplastic cells and inhibiting their progression to malignancy**.** This immune modulation halts the progression of potentially malignant lesions like leukoplakia. Topical 5% imiquimod provides excellent results in non-homogenous leukoplakia than homogeneous leukoplakia. Buccal mucosa showed most satisfactory regression of lesion. This suggest that lesion, site, size & dysplasia has significant role in prognosis of the lesion. Imiquimod the best alternative to conservative management of moderate to severe dysplasia cases and it's also better than a surgical option where surgery leads to more morbidity.

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