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RESEARCH ARTICLE

EFFECTIVENESS OF NON-SURGICAL TREATMENT OF LEUKOPLAKIA: A PROSPECTIVE STUDY FROM A TERTIARY CENTER IN NORTH INDIA

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ABSTRACT

Background: Leukoplakia is the most common potential malignant disorder found in the oral cavity. There are several factors considered for its management such as habits, size, and site of lesion, type, clinical features, and histopathological features in order to prevent the malignant transformation of leukoplakia. Till date, many studies have been conducted, where only few have mentioned the correct management of Oral Leukoplakia (OL). Thus there is a need for a protocol in the non-surgical management of Oral Leukoplakia. So, the aim of this study was to assess the effectiveness of non-surgical treatment of oral leukoplakia (OL). Materials and Methods: Hundred Clinically and Histopathologically confirmed cases were included in the study. Cases were treated conservatively by using topical Clotrimazole 1% and capsule Lycorich for 10 days. Then patients were followed up for next 3 and 6 months. In this most common type of leukoplakic lesion, type of habit becoming the cause, size of lesion and amount of response to Non-Surgical treatment were assessed. Results: Most common type of Leukoplakia was Homogenous Leukoplakia (76%), majority of patients had smoking habit followed by combination of Alcohol and Smoking habit (30%): Tobacco chewing and Smoking habit (23%) and only Tobacco Chewing habit (7%). Responses after 3 months of treatment showed that only 30% of patient showed 50% response. Whereas after 6 months follow up - 28% patient showed complete clinical response (100%). Conclusion: Thus within limitations it can concluded that conservative treatment is an effective treatment modality and obtained a good clinical response in the regression of lesion.

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INTRODUCTION

World Health Organization (WHO) defined "potentially malignant disorders" (PMD) as the risk of malignancy being present in a lesion or condition either during the time of initial diagnosis or at a future date. It is of two subgroups 1) Precancerous lesion, a benign lesion with morphologically altered tissue, which has a greater than normal risk of transforming into malignancy (eg., Leukoplakia, Erythroplakia) and 2) precancerous condition, a disease or patients' habit that does not necessarily modify the clinical appearance of local tissues but is linked with a greater than normal risk of precancerous lesion or cancer development in that tissue(eg. Oral submucous fibrosis, oral lichen planus) (Amagasa, 2011; Neville, 2002). Although information regarding its prevalence is scarce,commonly found prevalence is 1–5%with age range of 50-59 years. In recent years5% of PMDs found below 30 years of age (Lodi *et al*., 2016). Term Leukoplakiais a white plaque of questionable risk having

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excluded other known diseases or disorders that carryno increased risk for cancer (Warnakulasuriya, 2007). There are two main forms- 1) Homogeneous- (predominantly white area of uniform flat, thin appearance, smooth, wrinkled or corrugated surface throughout the lesion); 2) Non-homogeneous-(shows mixture of white-and-red lesion that may be either irregularly flat, nodular, or verrucous) (Van der Waal, 2002). Global Prevalence of oral leukolakia has been reported as 1-4%, while itstransformation to malignancy unlikely exceeds 1% of cases (Greenslade, 2017). Men and women are more or less equally affected with greater predilection of older and elderly men thus depicting its prevalence increases with age.Histopathologically, Leukoplakia displays as epithelium atrophy and epithelial hyperplasia. Varyingdegrees of epithelial dysplasia can be seen in some cases of leukoplakia (Van der Waal, 1997; Neville, 2002).

Aetiology of Leukoplakia always varies. Smoking is considered as one of the commonest factor, while alcohol is another risk factor with less definitive data (Warnakulasuriya, 2007; Axéll *et al*., 1996). Dental restoration and mechanical irritation are additional factors considered for the occurrence of Leukoplakia. In addition to these, conflicting results are seen regarding the human papilloma virus infection for causal of Leukoplakia (Brouns *et al*., 2002). Regarding the severity of malignancy, Leukoplakiawhich are located on the floor of the mouth, soft palate, and tongue are considered as high-risk lesions, while, in other areas, they may be consideredas of low malignancy risk (Lumerman, 1996; Zhang *et al*., 2001). Objective in oral leukoplakia's management is to detect and preventmalignant transformation. At first, the cessation of causative factors such as smoking and tobacco chewing are recommended. Further, the histopathological evaluation and the degree ofdysplasia willguide the choice ofthe treatment.In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended (Brouns *et al*., 2002). However, decision regarding the complete removal of low to moderate malignant riskleukoplakia mainly depends on factors such as location, size and patient's engagement in smoking cessation (for smokers) (Napier, 2008). Various types of surgical treatments are available for Oral leukoplakia such as conventional surgery, electrocauterization, laser ablation or cryosurgery. Recurrence rate of leukoplakia after surgical treatment has been reported as 10%–35% of all reported cases (Lodi, 2008). Nonsurgical treatment is also considered for the management of oral leukoplakia (Fernandes, 1997; Girod, 1996). This modality offers minimal adverse effects to patients, especially for patients with widespread leukoplakia that involves a large area of the oral mucosa or patients with medical problems and consequently high surgical risks (Hammersley, 1985). Additionally, potential advantages of the nonsurgical treatment of oral leukoplakiainclude easy application that does not require treatment at a medicalcenter with relative low cost (Epstein, 1998). Nonsurgical treatments of leukoplakia includesretinoids, carotenoids, lycopene and photodynamic therapy. Due to the lack of standard evidence of clinical effectiveness, present study aimed to evaluate thecurrent nonsurgical treatment options for leukoplakia.

MATERIALS AND METHODS

All patients reported to the Department of Oral Medicine and Radiology, Institute ofDental Sciences Bareilly were screened. 100 clinically and histopathologically confirmed cases of oral leukoplakia (homogenous and non- homogenous) based on the classification given by Warnakulasuriya's (2007) were included in our study. Based on following inclusion and exclusion criteria patients were recruited into the study- All patients reported with a white patch in oral cavity and where a diagnosis ofleukoplakia was made after complete clinical and histopathological examination were included.

Exclusion criteria

- Presence of dysplasia or invasive carcinoma on histopathology.
- Surgically managed patients.
- Patients with incomplete follow up.
- When examination was not possible due to trismus.

Approval for the conductance of the study was obtained through Institutional Ethical Committee and study was conducted according the Helsinki's Declaration 2000

Treatment rendered: Cases were treated conservatively by using topical ointment Clotrimazole 1% (3 times a day) and systemic medicine capsule Lycorich (1 cap BD) for 10 days. Then patients were followed up for next 3 and 6 months, where they were examined for most common type ofOL, History of Habit and to assess the change in the size of the lesion at the baseline and post treatment. Evaluation of the responses was assessed by quantitative measurement by measuring the size of the lesion using Vernier callipers, entire measurements were done at baseline and 3 months and 6 months respectively. These were determined through frequency distribution analysis.

RESULTS

In the present study 100 patients were treated having an age range of 22-63 years. Out ofthese 100 patients 82 were males and 18 were females with mean age group 44.32 years. In the present study, Common age group for leukoplakia is 36 to 55 (57%). Most common type of Leukoplakia was Homogenous Leukoplakia (76%), Prevalence of non-homogenous type of leukoplakia was only 24%. Regarding habit history, most common type of habit associated with Leukoplakia was smoking (40%).Present study revealed maximum number of patients had smoking habit followed by combination of Alcohol and Smoking habit (30%); Tobacco chewing and Smoking habit (23%) and only Tobacco Chewing habit(7%).
The most common size of lesion was 1x1 cm with its greatest dimensions ofabout 60% cases. The response ofthe cases that were treated conservatively wereassessed after 3 months and 6 months.Responses after 3 months of treatment showed a maximum response of 80% in 8% patients and minimum response of20% in 16% patients. Only 30% 0fpatient showed 50% response after 3 months follow up. Whereas after 6 months follow up28% patient showed complete clinical response (100%) and minimum response was 40% in 4% patients. Maximum number of patient showed (40%) 60% response after 6 months of conservative treatment.

DISCUSSION

Conservative treatmentutilises local and systemic chemo-preventive agents such as vitamins (vitamins A, C, E) and carotenoids (beta-carotene, lycopene). Carotenoids are the group of highly hydrophobic molecules with little/ no

solubility in water (Britton, 1995). Beta (β) - Carotene is a vitamin A precursor that is commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges (Mayne, 1996). Its use has been recommended for the prevention of potential malignant lesions, such as OL and protects against cancer because of its antioxidant action (Mayne, 1996). This action is expressed through ligation between beta-carotene and oxygen, resulting in an unstable reactive molecule that diminishes the damaging effects of free radicals (Kaugars, 1996). β -carotene has a better therapeutic response in preventing oralleukoplakic lesions in smokers than in non-smokers. Clinical resolution of the lesion is within the range of previous study conducted byErhardt, *et al*.; where they have reported that clinical resolution ofOL ranges from 4% to 54%, with dosages of 20 to 90mg/day (beta-carotene) for 3 to 12 months duration (Erhardt, 2002). Even Liede, *et al*. (1998) concluded that β -carotene prevented the changes in the oral mucosa, especially in smoker patients, who presented the low serum levels of vitamin C and beta-carotene when compared to non- smokers. Similarly present study reveals that maximum amount of response was shown through conservative treatment.

Results of the present study were better (28%) than previous study conducted by Garewal, *et al*. (1999) where they evaluated only 50 patients with OL, only 2 patients (4%) demonstrated a complete clinical response while relapse were found in 4 patients. Further second biopsy was done after 6 months in 23 patients. There was no change in the degree of dysplasia in 14, with improvement of at least 1 grade in 9 (39%). Study conducted by Sankaranarayanan, *et al*. (1997) revealed that 15 patients who used 360 mg of β -carotene per week for 12 months presented complete resolution in OL. But during follow up period, eight (54%) patients (previously complete resolved cases) presented recurrence. Lycopene is a fat-soluble red pigment found infruits and vegetables. Most common source of lycopene is tomatoes (Painter, 2003). In addition to its anti-oxidizing property, has the capacity to modify intercellular exchange junctions and considered to play a protective role against progression ofdysplasia by inhibiting tumour cell proliferation. A study evaluated lycopene in OL for a three months period, with dosages regimes from 4mg/day and 8mg/day and patients had clinical resolution 25 and 55%, respectively. It has been reported that a daily dose of8 mg of lycopene was more effective than 4mg a day (Aung, 2013). Even Zakrzewska (Zakrzewska, 2005) concluded that lycopene brings about histological changes of a significant degree in patients with OL. Present study is in accordance with Singh M, *et al*. (2004) where authors have concluded that supplementation oflycopene (8 mg/day and 4 mg/day) reduced hyperkeratosis (clinically measured by the size of the lesion) with a similar efficiency in 80% of the cases. The complete clinical response ofpatients receiving 8mg/day was 55% and 4 mg/day was 25%. In the present study 4 mg/day dosage showed a slight better result of complete clinical response of 28% at 6 months follow up. Thus there are no side effects of Lycopene in the treatment of OL (McClain, 2003; Agarwal, 2000; Bramley, 2000). Moreover it is a promising candidate in reducing cancer and chronic diseases in human beings. Studies conducted by Nagao T, *et al*. (2000) demonstrated that serum levels oflycopene in leukoplakic patients were relatively lower when compared to healthy individuals. Study conducted by Gupta PC, *et al*. (1998) utilized tomatoes as the source of lycopene and evaluated the efficacy of lycopene (nutrient intake) in the resolution ofOL.

In the present study there was utilization of tablets instead of natural sources as all patients will not consume tomatoes. Moreover till date there are no much studies conducted determining the efficacy of lycopene in the resolution of OL. Present study is one among them along with the previously published study. Present study does not reported any side effects and has better results when compared with previous study conducted by Kaugars CG, *et al*. (1996) where they have evaluated the retinoic supplementation in various dosages for OL treatment and finally concluded that 50% of patients had complete/ partial clinical resolution of OL, but with side effects such as dizziness and headache. In addition to this, recurrence was reported upon the discontinuance ofmedication and some patients discontinued the treatment also. Vitamin-E is the collective term for a family of chemicalsubstances that are structurally related to Alpha (α)-tocopherol (Aguilar *et al*., 2008). Ithas an anti-tumour proliferation capacity, functions as a free radical scavenger to prevent lipid peroxidation of polyunsaturated fatty acids. It is found in plant oil, margarine, and green leaves (Van Poppel, 1997). Lycorich Capsule that has been used in the study also contains 5 mg Vitamin-E. This Vitamin-E levels are very much important as any depletion of their levels lead to a weak anti-oxidant defense system and increased reactive oxygen species. Thus there is an increased vulnerability for DNA damage and disease progression. So, antioxidant supplement (vitamin C and E) may have role in oral cancer patients (Balwant, 2008).

Conclusion

Thus within limitations ofthe study conservative treatment of Oral Leukoplakia is an effective modality with complete clinical response in 28% patients in 6 months. But before starting the treatment, Dysplasia or in situ cancer should be ruled out. Another limitation of the study can be shorter time period. Further longer follow ups are necessary for better outcomes.

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