To Evaluate the Efficacy of Tissue Autofluorescence (Velscope) in the Visualization of Oral Premalignant and Malignant Lesions among High-Risk Population Aged 18 Years and Above in Haroli Block of Una, Himachal Pradesh

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INTRODUCTION

Oral malignant lesion has been found to be the most common head and neck malignancy in India. It is observed that the 5-year survival rate of oral squamous cell carcinoma patients have remained relatively low,
only approximately 50%-60%, and the rate is even lower when the patients are diagnosed at the later stages of the disease.\(^1\)

Given its high mortality and morbidity, early diagnosis is of utmost importance. Hence, screening of individuals at risk for malignant lesion and its precursor has potential for early detection and treatment, thereby improving survival.\(^2\) There should be a focus on the cancers which contribute the highest to disability-adjusted life-years (DALYs) in India, including lip and oral cavity cancers which are currently the focus of screening and early detection programmes.\(^3,4\)

In the absence of a definitive approach, screening of oral cancer is still largely based on conventional oral examination (COE) and scalpel biopsy in case of suspicious lesions.\(^5\)

Since visible changes in the oral mucosa are known to precede the development of virtually all oral squamous cell carcinomas (OSCCs), various adjunctive techniques have been introduced with the aim to assist in the detection of early cancerous mucosal changes that can be occult to visual inspection.\(^6-8\) Velscope which has been recently introduced utilizes the property of autofluorescence to help in the diagnosis of dysplastic changes.\(^9\) Autofluorescence examination of oral tissues with the use of the Velscope has been suggested as an adjunctive tool for oral cancer detection and diagnosis.\(^10,11\) The studies have shown that the diagnostic tools using the autofluorescence have the possibilities of \textit{ex vivo} diagnosis and noninvasive examinations for oral cancer.\(^12-17\) Despite this, there is a disagreement of various studies about its clinical effectiveness, and the diagnostic efficacy of this tool is still much debated in scientific and clinical medical literature.\(^18-20\) The availability of such efficient and effective tools from this point of view could help the in the early diagnosis, and also improving the quality of life of the patient by timely intervention, and in some cases guaranteeing a longer survival term.

Despite the continuous improvements made over time in order to eliminate the problems of sensitivity and specificity of the various methods, at present there are no predictable routine methods or large-scale screening programs.

The objective of this study was to evaluate the efficacy of the Velscope in detecting dysplastic or malignant changes in all the oral mucosal lesions by using biopsy and histopathology as “gold standard”, to compare the results of Velscope examination with white light examination / conventional oral examination (COE), and to evaluate the autofluorescence characteristics of these lesions by obtaining data on the autofluorescence pattern of a variety of benign, dysplastic and malignant oral mucosal lesions irrespective of their biologic behavior.

**Materials and Methods**

The community based prospective cross-sectional study was conducted over a period of 2 years (September 2018 to September 2020) in high-risk population with oral mucosal lesions aged 18 years and above who were residing in the geographical area of Haroli block of Distt Una, Himachal Pradesh. High risk was based on addicted to tobacco either in smoke (cigarettes) or smokeless form (gutka, betel nut chewing), excessive alcohol consumption. Haroli block of Una district has rural population of 1,05,597 which inhabits in 59 villages. Haroli has 21175 households and gender ratio of 1095/1000, according to the 2011 Census figures. There were approximately 75,000 individuals who are 18 years and above.

Before the beginning of the study, written informed consent was obtained from each patient.

The study was approved by the Institutional Ethics Committee.

**Inclusion criteria**

a) Oral premalignant lesion: (Leukoplakia, Erythroplakia, lichen planus or pemphigus vulgaris, Verrucous hyperplasia etc.)
b) Age 18–75 years

**Exclusion criteria**

a) Patients with current advanced squamous cell carcinomas
b) Foreseeable missing opportunity of follow-up examination
c) Dermatological diseases of the face

**Sample size**

Sample size was calculated by assuming the prevalence of oral mucosal lesions in high risk population as 20% because many previous studies had shown this estimate around 20%. Considering 95% confidence level and an absolute precision of 5%, the sample size of 246 was calculated.

The following simple formula was used for calculating the adequate sample size in this study, \(n=Z^2p(1−p)/d^2\)

Where \(n\) was the sample size, \(Z\) was the statistic corresponding to level of confidence, \(p\) was expected prevalence (that was obtained from same studies), and \(d\) was precision (corresponding to effect size).
SAMPLING PROCEDURE
A total of 3,800 high risk individuals (change in voice, burning sensation, lump in neck/oral cavity, ulcer, red or white patch, tooth or gum problem/bleeding and sore throat) were screened by ASHA workers. 950 subjects with suspicious oral mucosal lesions were included in the study. Out of 950 subjects, 250 (25%) subjects were randomly selected using systematic random sampling technique.

The conventional oral examination was done by trained field investigators for these subjects under white operatory light in Community Health Centers (CHC’s) and primary health centers (PHC’s), and a provisional clinical diagnosis was noted. Then the autofluorescence examination was followed for these participants using the Velscope (LED Medical Diagnostics Inc, Burnaby) [Figure 1].

Interpretation of visually enhanced lesion scope fluorescence:
Greenish fluorescence emanating from site was considered as indicative of normal and healthy mucosa. Dark/brownish color fluorescence observed through Velscope was considered as positive for dysplastic changes within the mucosa [Figures 2B and 3B]. Dysplastic tissues with significant keratinization (leukoplakia) could exhibit increased whiteness with loss of fluorescence (darkness) around the periphery of the lesion.[21,22]

All the lesions documented during COE and the Velscope examination, were subjected to future review and correlation.

On the basis of autofluorescence characteristics during Velscope examination, the lesions were divided into two groups.

Group 1 (fluorescence visualisation loss or FVL) included oral lesions that exhibited a loss of autofluorescence

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Field Implementation plan:

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Haroli Block ,Una
59 villages, 21175 Households

High Risk Individual Screening by trained ASHA workers through Household survey/ Oral Cancer Screening camps

3800 High Risk Individuals identified

950 subjects with suspicious oral lesions

250 Subjects selected

Clinical oral examination followed by VELscope examination at 7 PHC’s and 2 CHC’s of study area by dental surgeon/trained Field Investigator

Histopathologic examination at Dr.RPGMC, Hamirpur (HP)
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and appeared dark from the surrounding normal tissue with pale green autofluorescence thus, indicating dysplastic / malignant change.

**Group 2** (fluorescence visualisation retained or FVR) included oral lesions that showed retention of autofluorescence and exhibited no change in
autofluorescence when compared to the surrounding normal tissue.

Lesions were rated as malignant or dysplastic only when there was a complete FVL and lesions showing autofluorescence patterns other than a complete FVL lesions were included in the FVR group.

Incisional biopsy was done for oral lesions for histopathological diagnosis after obtaining informed consent. The biopsy sites were selected based on fluorescence loss. In case the Velscope test was negative, the site for biopsy was dictated by clinical examination. The dysplastic lesions were graded according to the number of dysplastic features exhibited into mild, moderate, and severe dysplasia. The comparison was done for the results of Velscope examination and the histopathological diagnosis [Figures 2A–C and 3A–C].

The result was considered as true positive when a lesion exhibited FVL and histopathologic examination showed malignant or dysplastic changes while a result were considered false positive when a lesion exhibited FVL and histopathological assessment showed benign changes.

A result was considered true-negative when the lesions showed FVR and histopathological assessment showed the lesions to be benign and the result was considered a false-negative when a lesion demonstrated FVR and showed malignant changes on histopathological assessment.

The sensitivity score of examination was noted as the proportion of malignant and dysplastic lesions that were correctly identified with the Velscopic examination while the specificity score of examination was noted as the proportion of benign lesions that were correctly identified with the Velscopic examination.

The positive predictive value (PPV) was noted as the proportion of lesions with positive Velscopic examination results that were correctly diagnosed as malignant on histopathological examination whereas the negative predictive value (NPV) was noted as the proportion of lesions with negative Velscopic examination results that were correctly diagnosed as benign on histopathological examination. The contingency table was used to calculate sensitivity, specificity, positive and negative predictive values.

**Data and Statistical Analysis**

The data on various outcomes were presented in form of proportions. The standard error of difference of proportion test was applied to detect significant difference between proportions. Level of significance was set at 5%. The median was used to compare non-uniformly distributed data.

**Results**

The median age of the participants in the study was 50 years and the Inter Quartile Range for age was 41 to 59 years. The maximum proportion of participants in the study were in the age group 40–60 years (52.4%) followed by the age group 20–40 years (23.6%). Also, most of the participants of the study were coming from the upper middle class comprising of a proportion of 42.4% followed by the lower class for which this proportion was found 34.8%. Figure 4 shows the classification of lesions on White Light Examination. Figure 5 shows the results of the Velscope examination. Group 1 included oral lesions that exhibited FVL on Velscope examination while Group 2 included those oral lesions which exhibited FVR. Few of the lesions examined in the study exhibited autofluorescence patterns other than FVL and FVR. These lesions showed either fluorescence visualization increase or FVI (lesional area exhibiting increased autofluorescence compared to the surrounding tissue) and a combination of FVL and FVR (lesional area exhibiting patches of FVL as well as FVR) or FVI and FVR (lesional area exhibiting patches of FVI as well as FVR). As there were no specific criteria to characterize these lesions based on their autofluorescence patterns, these lesions were considered in FVR group for the purpose of

![Figure 4: Classification of outcomes after white light examination of lesions](image-url)
In order to describe the groups based on their autofluorescence characteristics, Group 2 lesions were further classified into four subgroups as; Group 2(i) (lesions exhibiting FVR), Group 2(ii) (lesions exhibiting a combination of FVL and FVR), Group 2(iii) (lesions exhibiting FVI) and Group (iv) (lesions exhibiting both FVI and FVL) with total number of 25, 56, 55 and 0 lesions each group respectively [Table 2].

Group 2(i) included 23 (92.0%) benign and 2 (8.0%) malignant lesion, Group 2(ii) included 51 (91.07%) benign and 5 (8.92%) malignant lesion, and Group 2(iii) included 50 (90.90%) benign and 5 (9.09%) malignant lesions [Table 2].

Out of the 250 cases, the white light examination had classified 217 (86.80%) cases as positive and 21 (8.40%) cases as negative while there were 12 (4.80%) such cases in which the white light examination failed to detect the case into positive and negative categories. While the test considered as gold standard i.e., histopathological examination had detected 48 (19.20%) lesions as malignant and 202 (80.80%) lesions as benign [Figure 4].

The Velscope findings of 250 oral mucosal lesions showed that Group 1 comprised 114 (45.6%) oral lesions while the remaining 136 (54.4%) lesions were of Group 2 [Figure 5].

On histopathological assessment, there were 202 (80.80%) benign lesions and 48 (19.60%) lesions were malignant. Amongst these, 77(67.54%) were benign and 37 (32.45%) were malignant lesions in Group 1 whereas, 124 (91.17%) were benign and 12 (8.82%) were malignant lesions in Group 2 [Table 2 and Figure 5].

The comparison of the Velscope results with the histopathological diagnosis showed the number of lesions with true-positive, false-positive, true-negative and false-negative values as 36 (14.40%), 78 (31.20%),
Table 2: Comparison of the VELscope findings with histopathology

| Group      | No. of lesions | Malignant                                     | Histopathological diagnosis          | Benign                                     | No. of lesions |
|------------|----------------|-----------------------------------------------|---------------------------------------|--------------------------------------------|----------------|
| 1(FVL)     | 114            | Oral Squamous cell carcinoma                  | 32(28.07%)                            | Oral Submucous Fibrosis                    | 2(1.75%)       |
|            |                | Severe epithelial dysplasia                   | 4(3.50%)                              |                                            |                |
|            |                | Verrucous carcinoma                           | 1(0.87%)                              |                                            |                |
| 2(i) (FVR) | 25             | Oral Squamous Cell Carcinoma                  | 1(4.0%)                               | Leukoplakia                                | 4(16.0%)       |
|            |                | Severe epithelial dysplasia                   | 1(4.0%)                               |                                            |                |
| 2(ii)      | 56             | Oral Squamous Cell Carcinoma                  | 3(5.35%)                              | Oral Submucous Fibrosis                    | 43(76.78%)     |
|            |                | Severe epithelial dysplasia                   | 2(3.57%)                              |                                            |                |
| 2(iii)     | 55             | Oral Squamous Cell Carcinoma                  | 4(7.27%)                              | Leukoplakia                                | 48(87.27%)     |
|            |                | Severe epithelial dysplasia                   | 1(1.81%)                              |                                            |                |
| Total      | 250(100%)      | 37(32.45%)                                    | 77(67.54%)                            |                                            |                |

Table 3: Contingency Table for VELscope Results

| VELscope examination FVL-1, FVR-0 | Histopathology Examination: Positive-1, Negative-0 | Total |
|----------------------------------|---------------------------------------------------|-------|
| 0                                | 0                                                 | 124   |
| 1                                | 124                                               | 12    |
| 1                                | 78                                                | 36    |
| Total                            | 202                                               | 48    |

124 (49.60%) and 12 (4.80%) respectively while the sensitivity, specificity, positive and negative predictive values were, 75.00% (95% CI: 69.63%-80.37%), 61.39% (95% CI: 55.35%-67.42%), 31.58% (95% CI: 25.82%-37.34%) and 91.18% (95% CI: 87.66%-94.69%) respectively. The prevalence of Velscope results in high-risk group of patients was found to be 19.20% (CI:14.32%-25.07%). Also, the accuracy of the diagnostic test was 64.40% [Tables 3 and 4].

Further the 2×2 classification of White light results with the histopathological diagnosis revealed 36(14.40%) true positives, 181(72.40%) false positives, 21(8.40%) true negatives and 0(0.00%) false negative cases. These numbers in turn concluded with the sensitivity, specificity, positive predictive value and negative predictive value estimates for the white light examination as 100.00% (95% CI: 100.00%-100.00%), 10.40% (95% CI: 6.52%-14.27%), 16.59% (95% CI: 11.86%-21.32%) and 100.00% (95% CI: 100.00%-100.00%). The prevalence of white light examination results in high-risk group of patients was however found to be 15.13% (CI: 10.57%-19.86%). The accuracy of white light examination was 23.95% [Tables 5 and 6].

Figure 6 shows the ROC curves of White light examination and Velscope examination against the gold standard histopathological results. The ROC (Receiver Operating Characteristic) analysis revealed that the area under the ROC cover of White Light Examination is 55.20% whereas the area under the ROC curve of Velscope examination is 80.69%.
In the present study, 250 subjects with suspicious oral mucosal lesions were subjected to COE which followed Velscope examination. The comparison of autofluorescence characteristics of oral lesions was done with the histopathological examination. The sensitivity and specificity scores of the Velscope examination were 75.00% (95% CI: 69.63%-80.37%), and 61.39% (95% CI: 55.35%-67.42%), respectively while the positive and negative predictive values were 31.58% (95% CI: 25.82%-37.34%) and 91.18% (95% CI: 87.66%-94.69%) respectively when subjected to statistical analysis.

In a study of 200 patients conducted in Mumbai, it was found out that the Velscope examination showed sensitivity and specificity values of 76% (95% CI: 54.87–90.64%) and 66.29% (95% CI: 58.76–73.24%) respectively while the positive and negative predictive values were 24.36% (95% CI: 19.22–30.36%) and 95.08% (95% CI: 90.52–97.5.%) respectively.[12] This study was conducted in hospital based settings while we tried to test the feasibility of such a tool on a community wide level so that it could be estimated that if there is any kind of gain in early detection when this tool is implemented in a community. In a study by Hanken et al.[13] 120 patients with suspicious oral lesions were examined and the sensitivity and specificity values of the Velscope examination were noted as 22% and 8.4% respectively. Velscope was more promising than COE in detecting precursor oral malignant lesions in this study. Similarly, a higher sensitivity (97%) and specificity of (95.8%) of the Velscope in diagnosing OSCC were reported in a study by Koch et al.[14] The comparison
was done between Velscope examination with COE in a study by Rana et al., and it was found that Velscope showed higher sensitivity (100% vs. 17%), but a lower specificity (74% vs. 97%).

The results of autofluorescence study by Yan et al. using light -induced autofluorescence spectroscopy demonstrated that the sensitivity was >84%, the specificity was not < over 76% and the accuracy was about 80%, respectively. The recent review by Cicciu M et al. demonstrated the sensitivity and specificity results of the Velscope as 70.19% and 65.95%, respectively. The results of our study were similar to the results of these studies.

The high rate of false-positive results led to the high negative predictive value and a low specificity in our study whereas; the sensitivity of the Velscope examination is limited by the false-negative results. The ROC curve analysis was also conducted to determine the discriminatory performance of Velscope examination. The comparison of AUC’s (Area under the curve) of White Light examination and Velscope examination showed that Velscope performed better in discriminating the diseased from non-diseased (80.69% vs. 55.20%). The results of study by Yan et al. showed that the area under curve of the receiver operating characteristic (ROC) was achieved at about 87%, respectively. These studies showed the diagnostic tools using the autofluorescence has the possibilities of ex vivo diagnosis and noninvasive examinations for oral cancer.

The metabolic and biochemical status of the cells is said to be dictated by tissue autofluorescence. When exposed to light of a specific wavelength, the endogenous fluorophores produce florescent emission. The tissue autofluorescence is dependent on this phenomenon. There is an altered autofluorescence profile in malignant lesions as compared to normal oral mucosa which is due to alterations in endogenous fluorophores.

In Group 1 (lesions showing loss of autofluorescence), malignant as well as benign lesions showed FVL [Table 1]. While the malignant lesions are expected to show FVL, benign inflammatory lesions like pyogenic granuloma, fibro-epithelial hyperplasia, and central giant cell lesion also exhibited FVL which resulted in false-positive results in our study. The increased subepithelial blood flow and altered metabolic activity of the inflamed mucosa have been attributed for FVL in such cases. Thus, in addition to similarity between benign inflammatory lesions and a malignancy clinically, benign lesions may also demonstrate similar autofluorescence characteristics resulting in an overdiagnosis of malignancy. The development of invasive OSCC is usually preceded with early dysplastic changes. An alteration in the endogenous fluorochromes is caused by these changes which manifest as FVL. Contrary to this, in our study there is 1 case of severe epithelial dysplasia and 1 case of oral squamous cell carcinoma (OSCC) showing FVR, 3 cases of oral squamous cell carcinoma (OSCC) and 2 cases of severe epithelial dysplasia showing a combination of FVL and FVR in the same lesion, and 4 cases of OSCC and 1 case of severe epithelial dysplasia showing FVI [Table 2]. Thus, false-negative results were given by these lesions which affected the sensitivity of the device. These results of the study suggest that the Velscope cannot accurately differentiate between dysplastic and non-dysplastic lesions and are in agreement with various studies who stated that autofluorescence has low specificity for dysplasia and malignant lesions. 45 cases of oral submucous fibrosis (OSF) were included in the present study demonstrating both autofluorescence patterns with focal areas of FVL interspersed between areas of FVR [Table 2]. The combined autofluorescence pattern was noted in OSF in our study. Lesions showing FVR and both autofluorescence characteristics could be due to overlap in the wavelengths of healthy oral mucosa (between 375 and 440nm) and fibrosis (between 380 and 460nm) Physical and chemical irritation is caused by Areca nut and its metabolites which results in microtrauma and inflammation of the underlying mucosa. The focal areas of FVL seen in OSF could be due to changes in metabolic activity of the inflamed mucosa. These lesions have a malignant transformation rate of 7–13%. Cases of OSF could not be correctly interpretation and the clinical judgement is difficult for the practitioner due to inconclusive autofluorescence characteristics, thereby, limiting the efficacy of the Velscope as an adjunct to COE. In our study, leukoplakia as well as OSCC exhibited FVI [Table 2].

The suspected malignant lesion exhibit FVL which is not applicable for these lesions and it resulted in false-positive results in our study. Thereby, the lesions showing FVI limit the ability of the Velscope to detect malignant change. The results of our study suggest that FVL is not a good indicator of the nature of oral mucosal lesions and that neither malignant or benign lesions. FVL nor FVR can exclusively show FVL or FVR. The results of our study also showed that a high negative predictive value of 91.18% (95% CI: 86.20%-94.47%) on Velscopic examination. It suggests that the Velscope can rule out rather than to indicate the presence of malignant
change. It attributes that Velscope can be effective as an adjunct in a general practice setting. The findings of recent studies indicate that although autofluorescence cannot be a substitute for COE, it can be used as a potential complementary diagnostic aid in surveillance of the high-risk patient population. \(^{[28-30]}\)

The recent metaanalysis suggested that auto fluorescence may help as an adjunct to histopathology in detecting the dysplasia initially and stop further progression to the carcinoma. \(^{[31]}\) There is no prospective trial in our knowledge which has confirmed that Velscope is effective in identifying lesions that were not diagnosed by conventional oral examination and palpation alone.

**Limitations**

Our study included a very few cases of oral premalignant lesions and OSCC due to the unwillingness of some patients to undergo a biopsy procedure. Hence, the true prevalence could not be calculated in these cases. The PPV and NPV are a function of the sample prevalence values so interpretation should be done cautiously. Although various studies have evaluated autofluorescence largely in Oral premalignant lesions and OSCC, \(^{[25-27,31]}\) the present study differs in that the benign lesions which showed clinically similar to malignant lesions, additionally exhibited FVL on Velscope examination. Further prospective trials are suggested with adequate follow up and to be confirmed with histopathological examination in a primary care setting to evaluate the efficacy of the Velscope as a screening tool in oral premalignant and malignant lesions. The lack of specific criteria to characterize lesions based on their autofluorescence patterns limits the interpretation of the results of Velscope. The use of this device as an effective oral cancer screening adjunct will find little support until these issues are resolved.

**Conclusion**

The study results showed the low specificity of the autofluorescence examination for differentiating dysplasias and malignant lesions from benign lesions in all. Thus, a definitive diagnosis as to the presence of dysplastic tissue change cannot be provided with the Velscope. But it is also noteworthy that the specificity of Velscope examination is significantly higher than conventional oral examination. Velscope is better equipped to rule out the presence of malignant change due to a high negative predictive value. However, limit its efficiency is limited by the false-positive results. It can be used to alleviate patient and practitioner concerns regarding a clinically suspicious oral mucosal lesion.

**Recommendations**

Velscope is definitely useful to improve clinical decision making about the nature of oral lesions and aids in decisions to biopsy the lesions of concern. A combined approach of Velscope examination and conventional oral examination may prove to be an effective diagnostic tool for early detection of malignant oral mucosal lesions. Further, it is recommended that this combination of diagnostic procedures should be targeted towards general community setting rather than high risk groups as the study results have not shown any better performance in the high-risk groups particularly.

**Acknowledgement**

I thank all the supporting staff of Model rural health research unit (MRHRU), Haroli, Una for their expertise and assistance throughout all aspects of our study; and National JALMA Institute of Leprosy and Other Mycobacterial Diseases (ICMR), Tajganj, Agra, India for financial support and their help in writing the manuscript.

**Financial Support and Sponsorship**

This study was supported by the National JALMA Institute of Leprosy and Other Mycobacterial Diseases (ICMR), Tajganj, Agra, India.

**Conflicts of interest**

There are no conflicts of interest.

**Authors’ contributions**

AS contributed to concept and design of study, acquisition of data or analysis, and interpretation of data; drafting the article or revising it critically; and final approval of the version to be published. AS contributed to concept and design of study, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically; and final approval of the version to be published. AKB contributed to drafting the article or revising it critically; and final approval of the version to be published. CG contributed to acquisition of data or analysis and interpretation of data and drafting the article or revising it critically. SM contributed to acquisition of data and MP contributed to acquisition of data and final approval of the version to be published. SM contributed to drafting the article and revising it critically.

**Ethical Policy and Institutional Review Board Statement**

Not applicable.

**Patient Declaration of Consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/
her/her images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**DATA AVAILABILITY STATEMENT**

Not applicable.

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