Original Article

Role of Chemiluminescence examination as non-invasive diagnostic tool in early detection of Leukoplakia

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ABSTRACT

Objectives: To assess the efficacy of Chemiluminescent light (Vizilite plus) in enhancing visualization and its ability to highlight Leukoplakia lesion.

Material and methods: This was a cross-sectional study done on 40 study subjects. Subjects were inducted into the study irrespective of age and sex based on the specific inclusion and exclusion criteria. The lesion parameters like the location of the lesion, the shape of lesion, the size, the extent, borders and the presence or absence of any adjacent satellite lesions were assessed under Incandescent light followed by Toluidine blue and Vizilite plus examinations. Histopathological examination results were considered as the gold standard and TBLU and CHEM outcomes were compared to them.

Results: Vizilite plus examination method was most effective in assessing the size, borders and shape of the lesions followed by Toluidine blue and Incandescent light examinations. Toluidine blue and Vizilite plus examination methods demonstrated the sensitivity of 100% and specificity of 97.3%. They also demonstrated PPV of 100% and NPV of 75% with reliable accuracy of 97.5%.

Conclusion: Chemiluminescent light is a stepping stone and has the potential to revolutionize the diagnostic protocol for patients with potentially premalignant lesions. The device can be used as a general oral mucosal examination system and may in particular improve the visualization of potentially premalignant lesions.

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1. Introduction

Oral squamous cell carcinoma is major cause of death and global health problem throughout the world. The incidence of oral cancer worldwide varies from 2 to 18% and in India it varies from 0.1 to 13.5%.¹ Oral Leukoplakia is one of the important potentially premalignant lesion of the oral cavity. Leukoplakia is thought to be

precursor lesion of Oral Squamous cell carcinoma.² It has been defined as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion. Leukoplakia is further classified as homogenous and non-homogenous types.³ Malignant transformation rate of Oral Leukoplakia varies between 1.1% to 11.7%.⁴ Prevention of malignant transformation is important as the 5-year survival rate of Squamous cell carcinoma is 50%,⁵ early detection of dysplastic changes in Leukoplakia lesions can reduce the morbidity and mortality rate.⁶

Tobacco is found to be the main etiologic factor and contains many carcinogens which are collectively called as tar. Tar is found to be highly toxic and carcinogenic.⁷ Leukoplakia is six times more common among smokers than among non smokers.⁸ Alcohol is another independent risk factor. Certain studies have revealed the possible role of Human Papillomavirus infection too.⁸

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To facilitate early detection of suspicious oral white lesions and dysplastic changes various clinical modalities are available like Toluidine blue test, Vizilite examination, VELscope and Brush biopsy. “Vizilite plus” is a recently introduced commercially available diagnostic tool devised for the early detection of potentially premalignant lesions and is based on the principle of Chemiluminescence.⁹

Vizilite plus is a painless, effective and fast procedure. The future of it is promising for the further development and evolution of oral-cancer diagnostic aids for enhancing the quality of the patient care.¹⁰ Chemiluminescence refers to the emission of light during a chemical reaction. The most well known diagnostic aid using this principle is the Vizilite[®] system (Zila Pharmaceuticals, Phoenix, AZ, USA) introduced in 2002. This product aims at enhancing certain features of a lesion, such as brightness and sharpness of its borders.¹¹ Use of the light stick is intended to improve the visual distinction between normal mucosa and oral white lesions. Normal epithelium will absorb light and appear dark whereas hyper keratinized or dysplastic lesions appear white.¹² To reduce the number of false positives, the system has now been combined with Toluidine blue stain (Vizilite Plus[®]).¹¹ Studies assessing Toluidine blue have shown a sensitivity and specificity ranging from 93.5 to 97.8% and 73.3 to 92.9%, respectively.¹³ Use of Toluidine blue as a diagnostic aid for oral precancerous and cancerous lesions has been widely reported in the literature. But there is less information regarding the use of Chemiluminescence. Hence, this study aims to evaluate the efficacy of Chemiluminescence examination along with Toluidine blue dye as a potentially premalignant lesions screening aid.

2. Materials and methods

This study was planned and designed in the department of Oral Medicine and Radiology, Hithkarini Dental College and Hospital, Jabalpur, Madhya Pradesh, India. The study was approved by Institutional ethical committee. 40 study subjects presenting with Leukoplakia lesions irrespective of age, sex were recruited in to the study from subjects attending outpatient department of Oral Medicine and Radiology, Hithkarini Dental College and Hospital, Jabalpur, Madhya Pradesh, India. Subject's demographic data along with case history were recorded in a specially designed proforma. Study subjects were recruited in to the study based on specific inclusion and exclusion criteria as shown in Table 1. The study purpose and procedure was explained to the patient and written consent was obtained. Each subject underwent a conventional soft tissue examination under Incandescent light followed by Toluidine blue test and Vizilite plus examination. Intra-oral examinations were conducted by two trained Oral Medicine specialists under routine Incandescent operatory light using two dental mirrors and gauze, with digital palpation. Followed by intra-oral examination the subjects underwent 1% acetic acid solution mouth rinse for 30–

60 s. All the lesion parameters like the location of the lesion, the shape of lesion, the size, the extent, borders and the presence or absence of any adjacent satellite lesions were obtained (Fig. 1). Lesions were photographed and data regarding the conventional visual examination were recorded. Secondly, TBLU screening procedure was performed by giving pre rinse solution of 1% acetic acid for 20 s to the subjects. This was followed by an application of pre-soaked swab of pharmaceutical grade 1% Toluidine blue, was applied over entire lesions. Dark staining lesions were considered as TBLU positive (Fig. 2) and those which did not take up the stain were considered TBLU negative. After that all parameters of the lesions were recorded. Then 20 s post rinse with water was given. This was followed by a post oral rinse with a 1% acetic acid solution for 30 s. Later on room lights were dimmed, the oral cavity was examined and each visually identified lesion was evaluated using a Chemiluminescent light. Examination with Vizilite plus was done according to the manufacturer's instructions. The subjects were asked to rinse their mouth with plain water and expectorate it after 1 min. The outer flexible capsule of the light stick was bent, breaking the inner fragile glass vial. The light stick was then shaken vigorously to mix the contents, and placed in the open end of the retractor and assembled. Vizilite plus capsule was activated and placed on the retractor. The suspected lesions that reflected the aceto-white light were considered Vizilite plus positive and lesions reflected dark (Fig. 3) were considered Vizilite negative. All parameters of the lesion were again recorded under Vizilite plus examination.

Fig. 1. Clinical view of lesion at buccal mucosa under Incandescent light.

Table 1

Inclusion and exclusion criteria of the study population.

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> 1. All the subjects irrespective of age, sex or socio economic background with the habit of cigarette smoking or use of tobacco in any forms. 2. Subjects diagnosed clinically having Leukoplakia. 3. Subjects who are willing to participate and approve the informed consent. 	<ol style="list-style-type: none"> 1. Subjects without any deleterious habits of tobacco usage. 2. Subjects with any systemic disorders or mentally unstable subjects. 3. Subjects with dentures, sharp teeth and with parafunctional habits. 4. Subjects with evidence of clinical lesions like Leukoedema, Linea alba buccalis or Fordyce's granules. 5. Subjects with presence of frank malignancy. 6. Any sub mucosal swelling or mass or benign tumour. 7. Subjects who are allergic to any ingredients of the Vizilite plus kit. 8. Subjects who are not willing to participate and approve the informed consent.

Fig. 2. Lesion after staining (dark blue) with 1% Toluidine blue.

Fig. 3. Aceto-white delineation of borders on Vizilite plus testing.

All clinically suspected lesions underwent biopsies irrespective of the findings with TBLU and the results of CHEM protocol. Identified white lesions of study subjects were subjected to punch/incisional biopsy. Tobacco cessation was reinforced. Subjects were recalled for follow-up of healing biopsy sites. Histopathological

results were considered as the gold standard and TBLU and CHEM outcomes were compared to them. The data so gathered was sorted, tabulated and entered in a master chart. Later the data obtained was subjected to appropriate statistical analysis.

2.1. Statistical analysis

The data so obtained was sorted, compiled in a master chart and analyzed using SPSS version 10.5 software. Chi-square analysis, Mann Whitney *U* test and kruskal wallis tests were applied to compare if enhanced visualization of oral Leukoplakia lesions using Vizilite plus and Toluidine blue examination. For the purpose of determining the sensitivity and specificity information of all the three different diagnostic modalities was calculated by applying Receiver operating curve method.

3. Results

This study involved 40 subjects of Leukoplakia with mean age of 47.25 ± 8.89 years (mean $\pm$ standard deviation). Maximum incidence was found to be in the age group of 39–70 years. The study comprised of 38 males (95%) and 2 females. Among the study subjects 27 (67%) were tobacco chewers and 13 (32.2%) were smokers. Buccal mucosa was the most common site involved in our study 22 subjects (55%) followed by commissures 14 subjects (35%), labial mucosa 2 subjects (5%), tongue 1 subject (2.5%) and palate 1 subject (2.5%).

The results of our study indicated that Vizilite plus examination method emerged as a best method in assessing the size, shape and borders followed by Toluidine blue and Incandescent light examination methods (Tables 2–4). Table 4 depicts the mean and standard deviation for assessing the of shape of Leukoplakia lesions by using Incandescent light, application of Toluidine blue and Vizilite plus examinations amongst the 40 study subjects. Incandescent examination revealed ill defined shape in 35 (87.5%) of subjects and well defined shape in 5 (12.5%) of subjects. Toluidine blue examination revealed ill defined shape in 18 (45%) of subjects and well defined in 22 (55%) of subjects. Vizilite plus examination revealed ill defined shape in 5 (12.5%) of subjects and well defined in 35 (87.5%) of subjects. Chi square test applied showed highly significant difference in assessing the shape of Leukoplakic lesions with all three diagnostic modalities [*p* value = 0.001** ($p \leq 0.0$)]. Chi square test applied for comparison showed that Vizilite plus is most effective in assessing the shape of the lesion followed by Toluidine blue and Incandescent light. However other parameters like texture, surrounding mucosa, biopsy sites were not affected and no new lesions were detected. Sensitivity and specificity was calculated by applying Receiver operating characteristic (ROC) curve method. Results obtained by Incandescent light method demonstrated sensitivity of 100% and specificity of 0.00%. The Toluidine blue method demonstrated the sensitivity of 97.30% and specificity of 100%. The Vizilite plus method demonstrated the sensitivity of 97.30% and specificity of 100%. Toluidine blue examination and Vizilite plus examination methods detected overall 36 true positive, 0 false positive, 1 false

Table 2

Intergroup comparison of different diagnostic modalities for assessing the size of Leukoplakia lesions.

Variables	Incandescent light (Mean $\pm$ SD)	Toluidine blue (Mean $\pm$ SD)	Vizilite plus (Mean $\pm$ SD)	Chi sq value	p-value
Size in cm ²	1.37 $\pm$ 0.42	1.45 $\pm$ 0.48	1.76 $\pm$ 0.69	7.074	0.029 [*]
Kruskal Wallis Test	* <i>p</i> $\leq$ 0.05 (significant difference)				

Table 3

Intergroup comparison of different diagnostic modalities for assessing the borders of Leukoplakia lesions.

Groups	Border appreciable n (%)	Border moderately appreciable	Border highly appreciable	Total	p-value
Incandescent light	40 ⁺ (100)	00	00	40	0.001 ^{**}
Toluidine blue	16 ⁺⁺ (40)	24 (60)	00	40	
Vizilite plus	00 ⁺⁺⁺	09 (22.5)	31 (77.5)	40	
Kruskal wallis Test	*p ≤ 0.001 (highly significant difference)				

Table 4

Intergroup comparison of different diagnostic modalities for assessing the shape of Leukoplakia lesions.

Groups	Shape ill defined n (%)	Shape well defined n (%)	Total	p-value
Incandescent light	35 (87.5)	5 (12.5)	40	0.001**
Toluidine blue	18 (45)	22 (55)	40	
Vizilite	5(12.5)	35 (87.5)	40	
Chi square test	*p ≤0.001 (highly significant difference)			

Table 5

Correlation between TBLU/Vizilite plus and Histopathological examination.

		Biopsy		Total
		Positive	Negative	
TBLU/Vizilite	Positive	36	0	40
	Negative	1	3	0
Total		37	3	40
PPV (%)		–	–	100%
NPV (%)		–	–	75%
Accuracy (%)		–	–	97.5%

negative and 3 true negative subjects. They also demonstrated PPV of 100% and NPV of 75% with reliable accuracy of 97.5% (Table 5).

4. Discussion

Improvement in early detection and diagnosis of precancerous changes and early treatment asymptomatic cancers is an advantage to increase survival rate of patients. The International Agency for Research on cancer (IARC) and World Health Organization (WHO) have stressed that one third of a predicted 15 million cancer cases in future can be reduced and more effectively manage another one third by implementing effective cancer control and screening strategies (IARC, 2002; Eaton, 2003).¹⁴ A Conventional Oral Examination, using normal (Incandescent) light, has long been the standard method for oral cancer screening. But the Incandescent light examination has limited by subjective interpretation and by the potential occurrence of dysplasia and early Oral Squamous cell carcinoma within areas of normal-looking oral mucosa. Toluidine blue is metachromatic vital dye that has been used effectively as a nuclear stain because it binds with DNA material.¹⁵ With increased advancement in technology, the dental profession has developed an Vizilite plus diagnostic tool for oral cancer screening that aids in early detection.

The observations found in our study were in accordance with the studies conducted by Epstein JB et al.¹⁶ and Awan KH et al.¹⁷ They found similar results on 84 and 70 subjects respectively. They demonstrated that Chemiluminescence examination enhanced the brightness, sharpness and size of lesions. Lesion brightness and sharpness were improved in 61.86% and 75.4% of the subjects. Suyambukesan S et al.¹⁸ conducted study on 70 patients, complete oral examination was performed for all the patients with normal Incandescent light and Vizilite. According to them no additional lesions were detected in normal subjects, no extra focal areas of

lesions were detected in potentially premalignant lesions of the study subjects and there was no change in the biopsy site after Vizilite examination. The results of their study were in accordance with our study, as our study too did not detect any new lesions nor there was alteration of biopsy site selection.

Farah CS et al.¹⁹ conducted a study on 55 subjects with Vizilite examination and opined that there was no significant difference in lesion size, ease of visibility, and border distinctness of the oral lesions examined. The results were not in agreement with our study.

Our study, compared sensitivity and specificity of each diagnostic tool with that of histopathological examinations. Results obtained by Incandescent light method demonstrated sensitivity of 100% and specificity of 0.00%. The Toluidine blue method and Vizilite plus methods demonstrated sensitivity of 97.30% and specificity of 100%. Our study results imply that both Toluidine blue and Vizilite plus methods are highly efficient and reliable methods for screening the potentially premalignant oral lesion such as Leukoplakia. The high index values of sensitivity and specificity can be attributed to the selection of subjects. Our study recruited 40 subjects of Leukoplakia only based on clinical diagnosis. Sensitivity indicates true positivity of the diagnostic tool. Specificity indicates true negativity of diagnostic tool. Incandescent light examination did not show any true negative result therefore specificity value 0.00% was obtained.

After going through the English literature we did not find any publications testing all the three diagnostic tools viz; Incandescent light, Toluidine blue and Vizilite matching our results. We found one publication whose results matched with our study. The study conducted by Suyambukesan S et al.¹⁸ conducted study on 70 subjects, among them, 50 were identified to have oral potential disorders and the remaining 20 subjects had no apparent lesions. Vizilite examination showed 100% sensitivity and 100% specificity for Leukoplakia. But, the examination results were not quite sensitive for Lichen planus and Oral submucous fibrosis.

However, a study done by Ramanathan A et al.²⁰ demonstrated similar results of sensitivity and specificity values but matched partially with our study results. They conducted a study on 20 subjects of potentially premalignant lesions. They found 55.5% sensitivity and 91.6% specificity with Toluidine blue method and Vizilite method demonstrated 88.8% sensitivity and 54% specificity.

The results of the study conducted by Farah CS et al.¹⁹ was not in accordance with results of our study the sensitivity was 100% and specificity was 0%, when Vizilite examination was correlated with histopathological examination.

The wide range of difference in sensitivity and specificity values observed in above cited studies could be attributed to wide spectrum of lesions present in the study subjects. Their subjects comprised of potentially premalignant lesions such as Erythroplakia, Lichen planus, Oral submucous fibrosis, Keratotic lesions and Oral Squamous cell carcinoma. Most of the studies which comprised Leukoplakia and Oral Squamous cell carcinoma yielded more positive results with Vizilite examination.

Though the correlation and accuracy of all three diagnostic tools with histopathological examination was not in our objective but still we were curious to find out Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy of the testing tools.

When Incandescent light examination was correlated with Histopathological examination method, Incandescent light examination method yielded PPV of (90%), NPV of (100%) with accuracy of 90%. When TBLU and Vizilite plus examination methods were correlated with Histopathological examination both methods yielded PPV of (100%) and NPV of (75%) with accuracy of 97% (Table 4). This was in agreement with study conducted by Sharma N et al.¹ they obtained PPV of (65%) and NPV of (66%) for Toluidine blue examination and for Vizilite examination they obtained PPV of (76.2%) and NPV of (75.9%). However, result values obtained by them were slightly lesser than our study. Ram S et al.²¹ demonstrated accuracy of 64.5% for Toluidine blue and 80.6% for Vizilite examinations.

The limitation of our study is that we have considered only Leukoplakia lesions and did not include other lesions such as Erythroplakia, Lichen planus, Oral submucous fibrosis, Keratotic lesions and Oral squamous cell carcinoma which could have undermined the results of sensitivity and specificity. Although major limitation of Vizilite examination are it needs a dark environment, no permanent record can be maintained unless photographed and also has high procurement cost. The fact is that it can be used only once for each patient. The disadvantages of Toluidine blue is that it gives information about surface changes, false retention of dye leads to wrong diagnosis and may cause burning sensation of mucosa. But this method is very cost effective when used it separately for selection of biopsy sites.

The results of our study inferred that both Toluidine blue and Vizilite plus examination method are highly reliable tools for screening of Leukoplakia. Based on our study we highly recommend using these two tools for the mass screening of Leukoplakia lesions in high risk populations. Further, more studies are required to evaluate the full potential of Vizilite plus as a diagnostic adjunct in early detection of dysplastic lesions. However, longitudinal case controlled studies with stricter inclusion and exclusion criteria in larger population are required to convert this potential tool into routine clinical application.

5. Conclusion

Based on the observations from our study it can be inferred that conventional examination by Incandescent light appears to be of limited success in case of potentially premalignant lesions. Toluidine blue has only adjunctive utility in diagnosing and delineating dysplastic oral lesions. The interpretation of stain retention is very subjective, so well defined criteria for staining needs to be established. The present study substantiated that Vizilite plus examination can also be employed as an alternative potent non-invasive diagnostic tool. Thus Chemiluminescent light is a stepping stone and has the potential to revolutionize the diagnostic protocol for patients with potentially premalignant lesions. The device can be used as a general oral mucosal examination system and may in particular improve the visualization of potentially premalignant lesions.

Conflict of interest

The authors have none to declare.

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