

Review Article

Light Based Headways- An Innovation in Diagnosis

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ABSTRACT:

Detection of Oral Squamous Cell Carcinoma at an early stage and oral potentially malignant disorders is essential for medical and dental professionals to improve patient survival rates. Evidence based studies have shown that a prompt and accurate diagnosis is possible only by advanced diagnostic methods; and these serve as an adjunct to biopsy which is still considered as gold standard to diagnosis. New technologies have provided an exciting new array of clinical diagnostic tools for localising or emphasising abnormal mucosa in OPD clinics as well as medical/ dental offices. In recent decades, optical techniques utilising the principles of chemiluminescence and tissue autofluorescence have emerged to facilitate the early detection of any oral mucosal changes suspicious of malignancy or a predecessor stage of malignancy. The present systematic review of different studies (2004-2018) was done to investigate the efficacy of Vizilite (chemiluminescence) and Velscope (autofluorescence) for early detection of Oral Squamous Cell Carcinoma and oral potentially malignant disorders.

Key words: Autofluorescence; chemiluminescence, potentially malignant disorders.

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INTRODUCTION

The term cancer, by itself has evoked a sense of morbidity and mortality among the medical fraternity as well as in the general population. Cancer of mouth is a serious condition with just over half of the afflicted individuals surviving for over 5 years.¹ In India oral squamous cell carcinoma (OSCC) represents a major health problem accounting for upto 40% of all cancers and is most common cancer in females.² OSCC is a potential candidate for screening as majority of these are thought to be preceded by Oral potentially malignant disorders (OPMDs) which if identified early and surgically removed, may reduce the incidence of malignant transformation.

OPMDs, namely leukoplakia and erythroplakia have a proportion of becoming overtly malignant, whereas the remainder may not become malignant within the life span of patient. Leukoplakia is a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion.³ and is most common OPMD with a world-wide prevalence of approximately 2.6%.⁴

Around 75% of OSCCs are linked to synergistic effect of tobacco use and excessive alcohol consumption, while

other factors include poor oral hygiene, irritation caused by ill fitting dentures and other rough surfaces of teeth, poor nutrition and some chronic infections caused by fungi, bacteria or viruses.⁵ Chewing betel pan and arecanut is a known strong factor for developing oral cancer.⁶ Despite these established risk factors and advances in treatment, the 5 year survival for OSCC associated with tobacco and alcohol use has remained consistently poor for the last forty years. Prognosis is further complicated by the high rate of second primary tumors, which is thought to be the result of field cancerisation in the upper aerodigestive tract.⁷

Screening is the process of identifying apparently healthy people who may be at increased risk of a disease or condition.⁸ It involves checking for the presence of disease in a person who is symptom free, with the intention of diagnosing treatable conditions at the earliest stage.⁹ It is believed to reduce morbidity and increase the survival of patient.¹⁰ If the malignant lesions are detected early (Stage 1 or 3) treatment is less aggressive, resulting in reduced morbidity and approximately 80% survival.¹¹

Histopathological analysis plays a vital role for suspected lesions in oral cancer diagnosis.¹² On the other hand

screening tests which include conventional visual examination diagnostic adjuncts such as TOULIDINE BLUE and LIGHT BASED SCREENING METHODS, are provided for asymptomatic individuals to ameliorate the early detection of malignant or premalignant lesions¹³ that have undergone abnormal metabolic or structural changes which have different absorbance and reflectance properties when exposed to specific wavelength of light.⁷ Apart from these, many techniques to date have been reviewed so far eg. vital staining procedure (Toulidine blue light +Iugols iodine), Brush biopsy (oral CDx brush) and micronuclei analysis DNA ploidy and Light based techniques including chemiluminescence and autofluorescent imaging.¹⁴ Chemiluminescence includes vizilite, vizilite plus, microlux TM/DL and Autofluorescence includes velscope (visual enhanced lightscope)

The present systematic review of different studies (2004-2018) was done to investigate the efficacy of vizilite (chemiluminescence) and velscope (autofluorescence) for early detection of Oral Squamous Cell Carcinoma and oral potentially malignant disorders.

DISCUSSION

In 1978, working group of WHO classified precancerous disorders into lesions and conditions.¹⁵ Precancerous lesion or premalignant condition is a condition or lesion involving abnormal cells which are associated with an increased risk of developing the cancer.¹⁶⁻¹⁸ Prevention and early detection of oral premalignant disorders have the potential of not only decreasing the incidence of survival of those who develop cancer¹⁸but also decrease morbidity and mortality rate. The various methods used in the efficacy of light based material for detection of oral premalignant disorder are CHEMILUNISCENCE and AUTOFLUOROSCENCE. The search term used in Medline/Pubmed for autofluorescence were (autofluorescence or fluorescence or velscope) and (Oral or mouth) and (Premalignancy or Dysplasia or Malignancy or Cancer or Carcinoma or Neoplasm). The term used for Chemiluminiscence were (Chemiluminiscence or Vizilite or Vizilite plus or Microlux) and(Oral or Mouth) and (Premalignancy or Dysplasia or Malignancy or Cancer or Carcinoma or Neoplasm)

AUTOFLUOROSCENCE

Autofluorescence is a phenomenon where an extrinsic light source is used to excite endogenous fluorophores such as certain amino-acids, metabolic products and structural proteins.⁷ There are number of methods based on the principle of tissue fluorescence, which have been described for the use in oral cavity including Exogenous fluorescence, Autofluorescent spectroscopy and Autofluorescent imaging. Both exogenous fluorescence and Autofluorescent spectroscopy due to practical purposes are unlikely to be applied as screening aids therefore only autofluorescent imaging is acceptable in screening aids.

The velscope (Visual Enhanced Lesion Scope; Led Dental, White Rock, BC, Canada) is a commercially available hand – held device that exposes tissue to blue violet light (400-460nm). Normal tissue emits a pale green autofluorescence when viewed through a narrow band filter whereas neoplastic tissue is expected to cause Fluorescent Visualization Loss (FVL) and thus appear as dark area.¹⁹ Velscope system is the world’s leading oral cancer screening system. Although its mechanism of action can be supported biologically,whether it is able to distinguish between dysplasia and benign inflammatory lesion. Benign inflammatory conditions can result in an increased blood supply to a associated lesion. The increased hemoglobin content (chromophores) may absorb light and cause FVL that mimics neoplasia.²⁰ **Table 1** enumerates the advantages and disadvantages of velscope.²¹

Table 1: Advantages and disadvantages of Velscope

ADVANTAGES	DISADVANTAGES
<ul style="list-style-type: none"> •Non invasive •Painless 	<ul style="list-style-type: none"> •Psychological trauma for those with false negative results
<ul style="list-style-type: none"> •Minimal skills •Performed in large number 	<ul style="list-style-type: none"> •Only an adjuvant
<ul style="list-style-type: none"> •Patient compliance •Cost effective 	<ul style="list-style-type: none"> •Contamination
<ul style="list-style-type: none"> •Can be used in patient with systemic disorder where biopsy is contraindicated •Easily done at chair-side 	<ul style="list-style-type: none"> •Low sensitivity
<ul style="list-style-type: none"> •Reassurance for those screened negative •Minimal instrumentation 	<ul style="list-style-type: none"> •Inadequate sampling
<ul style="list-style-type: none"> •Early diagnosis of lesion 	<ul style="list-style-type: none"> •Not used in non-epithelial lesions

Table 2: Advantages and disadvantages of Vizilite

ADVANTAGES	DISADVANTAGES
<ul style="list-style-type: none"> • Vizilite was useful in enhancing the visibility and sharpness of oral leukoplakia 	<ul style="list-style-type: none"> •Examination needs a dark environment •High cost
<ul style="list-style-type: none"> • Making the clinical evident lesion more prominent and distinct from surrounding oral mucosa. 	<ul style="list-style-type: none"> •No permanent record unless photographed •Low specificity for dysplasia •Contributing to high referral rate and over-treatment
<ul style="list-style-type: none"> • 50% of erythroplakia lesions were Vizilite positive 	<ul style="list-style-type: none"> •Unable to detect some red lesions •Acetic acid pre-rinse increases salivary flow that interferes with mucosal surfaces reflectance
	<ul style="list-style-type: none"> •Inability to objectively measure the visualisation results •It gives adjunct information only about the horizontal extent of the lesion •Malignant behaviour cannot be assessed

Table 3: Summarizes the studies to evaluate the efficacy of tissue autofluorescence imaging (Velscope) in Detecting Oral Cancer and Oral Premalignant Disorders

Author (year)	Study design	Sample selection criteria	Inference		
			Sensitivity	Specificity	Conclusion
Canjau et al. 2018 ²⁷	Cross sectional study	Oral lesions (18 patients)	94.4%	100%	Excision of tissue with the help of Velscope. It helps in clearly marking the molecular margin when excising PMD's
Huang et al. 2017 ²⁸	Cross sectional study	Premalignant disorder 54 (OSCC 47, normal oral mucosa 39 (140 patients)	98.3%	77.6%	Use of quantitative analysis of autofluorescence were developed to solve the problem. Inter-observer variability method like quadratic discriminant analysis or luminescence ratio were promising
Ganga et al. 2017 ²⁹	Cross sectional study	Oral lesions (200 patients)	76%	66.3%	Limiting the utility of autofluorescence for oral squamous cell carcinoma
Yamamoto et al. 2017 ³⁰	Cross sectional study	Premalignant disorder, oral squamous cell carcinoma (62 patients)	85.9%	26.7%	No need of technical measures such as the use of dimmed light pre rinse or lesion. Use of quantitative analysis of autofluorescence were developed to solve the problem inter-observer variability method like quadratic discriminant analysis or luminescence ratio were promising
Amirchaghmaghi et al. 2016 ³¹	Cross sectional study	Pre-malignant disorder, OSCC(21 patients)	90%	15%	It is not able to differentiate between benign lesions from malignant and dysplastic because it has low specificity.
Ohnishi et al. 2016 ³²	In vitro study	Oral squamous cell carcinoma (60 patients)	91%	100%	Significant changes in autofluorescence pattern during progression to dysplasia and carcinoma
Jane-Salas et al. 2015 ³³	Pilot study	Oral lesion (60 patients)	40%	80%	The sensitivity does not get better significantly with the use of VELscope
Kaur and Jacobs et al. 2015 ³⁴	Cross sectional study	Oral lesion (130 patients)	67%	62%	Combination approaches of tissue autofluorescence and salivary protoporphyrin IX levels seems to be effective to distinguish between normal mucosa and high risk lesion
Sawan and Mashlah et al. 2015 ³⁵		Oral lesion (71 patients)	100%	74.1%	VELscope is a diagnostic tool used in detection of OPMD's and OSCC.it helps in detection of border in biopsy and its excision
Hanken et al. 2013 ³⁶	Single blinded study	Oral-Premalignant disorders (120 patients)	97.9%	33.3%	VELscope device is simple non- invasive test of oral mucosa which can help the experienced clinician to find oral premalignant lesion
Rana et al. 2012 ³⁷	Cross sectional study	Oral premalignant lesion disorder(123 patients)	100%	74%	VELscope is likely to lead over diagnosis if used by a non-specialist
McNamara K et al. 2012 ³⁸	Cross sectional study	Oral squamous cell carcinoma, oral premalignant lesion disorder (130)	Not reported	Not reported	FVL in one malignant and one dysplastic lesions ; VELscope has the potential for the false negative and has high false positive rates
Scheer et al. 2011 ³⁹	Prospective study	OSCC (41 patients)	100%	80.8%	It has low specificity values highlighting this as the primary limitation of VELscope
Paderni et al. 2011 ⁴⁰	Cross sectional study	175 patients (Benign disorder 118, mild dysplasia 15, moderate/severe dysplasia 14, OSCC 28)	OSCC 96.4% Dysplasia 71%	Not reported	Device doesnot reduce Histopathologically procedure
Koch et al. 2011 ⁴¹	Prospective blinded clinical trial	78 (OSCC 30, dysplasia 3, benign 45)	OSCC 93%	16%	Autofluorescence unstable to differentiate between benign and malignant lesion. Lesions with red color autofluorescence should be biopsied
Awan et al. 2011 ⁴²	Cross sectional study	126 patients oral premalignant /benign 61 Leukoplakia, 9 Erythroplakia, 32 Lichen Planus, 9 Hyperplastic Candidiasis, 2 OSMF, 44 Dysplasia, 56 Benign Lesions	Vizilite 100% T-blue 59% Dysplasia 77.3% Leukoplakia/erythroplakia 77.1%	Dysplasia 27.8% Leukoplakia/ Erythroplakia 26.8%	In patients of Oral Premalignant or OSCC reported low specificity values highlighting this as the primary limitation of VELscope
Mehotra et al. 2010 ⁴³	Cross sectional study	156 (OSCC 1, benign lesion 144, dysplasia 11)	50% ; OSCC 100%; dysplasia 45%	38.9%	VELscope does not add any benefits to a conventional screening examination with a standard overhead light

Table 4: Summarizes the studies to evaluate the efficacy of chemiluminescence (vizilite) in detection of oral cancer and oral premalignant disorder

Author (year)	Study design	Sample selection criteria	Inference		
			Sensitivity	Specificity	Conclusion
Chaudhary et al.2016 ⁴⁴	Cross sectional study	Oral Premalignant disorder (100patients)	84.2%	41.2%	According to it the results of a clinical study suggested that although the adjunct of TB to Vizilite reduced the false positive cases without increasing the number of false negative.
Kammerer et al.2015 ⁴⁵	Cross sectional study	Oral premalignant disorder (44 patients)	100%	30%	VL examination could show all malignancies with low specificity.
Vashisht et al.2014 ⁴⁶	Cross sectional study	Oral premalignant disorder and OSCC(60)	95.5%	84.6%	It stated that authors described the better diagnostic accuracy of Vizilite with respect to TB staining alone
Rajmohan et al.2012 ⁴⁷	Cross sectional study	30 patients (10-oral squamous cell carcinoma, 9-dysplasia,1-benign, 10-normal	Dysplasia 77.8% Oral squamous cell carcinoma 90%	Not reported	Vizilite is sensitive to premalignant disorder and malignant lesions is keratotic or red or white lesion
Mojsa et al.2012 ⁴⁸	Cross sectional study	34 patients (no dysplasia patients , severe dysplasia 3, mild dysplasia 3, OSCC 1	81.8% in TB staining; not reported in Vizilite	37.5% in TB staining; not reported in Vizilite	It does not seem to be useful to detect malignancies in patients with clearly visible lesion
Ujanoey et al.2012 ⁴⁹	Cross sectional study	50 patients Oral premalignant disorder/benign	Not reported	Vizilite 1% Tblue79%	Conclusion: Toluidine blue retention test may be better suited than chemiluminescence to detect high-risk oral precancerous lesions in a high-prevalence and low-resource setting like india
Mehrotra et al. 2010 ⁴³	Cross sectional study	102 patients (1 OSCC, 3dysplasia, 98 benign)	OSCC 0% Dysplasia 0%	Specificity 75.5%	It was a cross sectional study comparing Vizilite and VELscope to evaluate their clinical utility in diagnosing oral lesions but the authors were failed to demonstrate any superiority to COE
McIntosh et al. 2009 ⁵⁰	Cross sectional study	50 patients (2 OSCC, 7 dysplasia, 41 benign)	Dysplasia /OSCC 77.8%	Specificity 70.7%	Appears useful at enhancing lesion visibility, it is a poor discriminator for inflammatory, traumatic and malignant lesions.
Epstein et al.2008 ⁵¹	Cross sectional study	84 (9 OSCC, 4carcinoma insitu, 41 dysplasia, 43 benign)	Not reported	Not reported	It was done to improve the diagnostic power of TB marking system. According to this study TB reduced the number of false positive cases leaving the false negative rate unchanged
Farah and McCullough et al. 2007 ⁵²	Cross sectional study	55 (1OSCC 9 dysplasia 45 benign lesions)	Oral squamous cell carcinoma 100% Dysplasia 100%	Specificity 0%	Results has not been confirmed which failed to demonstrate significant improvement in identification and evaluation of oral lesion
Ram S et al 2005 ⁵³	Cross sectional study	46(14 OSCC, 26 OPMD, 6 benign)	Outcome sensitivity 100%	Specificity 14.2%	It appears to be a better diagnostic tool than toluidine blue in detection of OSCC and OPMD
Huber et al.2004 ⁵⁴	Pilot study	150 (oral lesion including benign)	Not reported	Not reported	Vizilite identified a subclinical lesion suggesting its utility in identifying occult epithelial abnormalities

CHEMILUMINESCENCE

Chemiluminescence involves emission of light from a chemical reaction between hydrogen peroxide and acetylsalicylic acid inside a capsule light stick.⁷ In 2002 vizilite became the first device approved by FDA for this purpose. It is a disposable capsule formed by an outer shell of flexible plastic containing hydrogen peroxide. To activate it, the capsule is bent to break the inner glass vial triggering the reaction of the chemicals contained in the two compartments. Consequently a bluish white light (430-580nm) is produced that lasts for 10 minutes.²² Sensitivity and specificity is about 77.3% and 27.8% respectively. It has been used in the examination of cervical mucosa for many years due to its ability to detect aceto-white premalignant and malignant lesions²⁰

One of the components of chemiluminescent examination is acetic acid pre rinse. It is mainly done to remove the debris and glycoprotein layer for enhanced penetration and reflection of light. But acetic acid is also known to cause cellular dehydration and protein coagulation that reduces the transparency of epithelium. This could be one of the reasons for aceto-white appearance of premalignant white lesions.²³ Chemiluminescence increases the brightness and margins of oral mucosal lesions thus assisting in identification of lesions which are not detected under conventional visual examination.⁷ Vizilite is the technology which is being used to find the effectiveness in detecting the soft tissue abnormalities in various parts of the body.

It is essential for people who are more susceptible to oral cancer. Vizilite is a combination with regular visual examination providing the comprehensive oral screening procedure for the patients who are at high risk for oral cancer. Vizilite is painless, effective, and a fast life-saving procedure. The procedure to use Vizilite is described as, patient is asked to do 1 minute mouthwash with acetic acid solution in order to dry the oral mucosa and for removing glycoprotein barrier. The intensity of focused light is dimmed and defused bluish white chemiluminescent light is applied which shows normal cells that can absorb the light and are depicted in the bluish color. The abnormal cells reflect the light back with the high nuclear-cytoplasmic ratio and the epithelium with hyperkeratinisation and predominant inflammatory infiltrate appears aceto-white color with more brightness and distinguished border.²⁴ It can be used with or without vizilite plus accessory eyewear depending upon the operatory environment. The vizilite plus accessory eyewear consist of lenses that filters the ambient light outside. The wavelength transmission range of chemiluminescent light is 430-580nm. Any lesion which is seen with Vizilite may show pathological and clinical implication that should always prevail for deciding the further analysis and management of premalignant and malignant lesion.²⁵ **Table 2** enumerates the advantages and disadvantages of vizilite.^{24,26}

Table 3 and 4 summarizes the studies to evaluate the efficacy of tissue autofluorescence imaging (Velscope)

and chemiluminescence (vizilite) in detection of oral cancer and oral premalignant disorder

CONCLUSION

Vizilite and Velscope are simple non-invasive technologies for early detection of Oral Premalignant Disorders and Oral Cancer, and are best suited for clinicians with experiences, training and prove real time results. In literature, both techniques have been shown to enhance case detection of oral mucosa but lacking their ability to discriminate the high risk lesion. They show poor specificity, because the chemiluminescence system preferentially detect keratotic lesions over red lesions and the VELSscope device shows FVL is to benign keratosis and inflammatory conditions. Further studies are required to define the role of these adjunctive methods to diagnose suspicious lesions from a therapeutic and prognostic perspective.

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