Efficacy of the Autofluorescence-based Imaging System (VELscope™) in Detection of Oral Potentially Malignant Disorders

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Abstract **- The occurrence of oral potentially malignant disorders (OPMDs) has ascended in developing countries where the usage of betel quid chewing and tobacco is accustomed. Despite the developing advanced treatment procedures, malignant transformation rate of some of the OPMDs is considerably high (4 to 18%) according to the recent studies. Hence, adjunctive diagnostic aids for early detection of oral cancer have been developed to help the practitioners in identifying high-risk OPMDs. VELscope™ is a one of the diagnostic adjuncts, which is non-invasive, handheld device designed to visualize early mucosal changes using the principles of tissue autofluorescence. The objective of the study was to determine the efficacy of VELscope™ in detection of OPMDs. Fifty-seven patients with OPMDs seeking treatment at University of Dental Medicine, Yangon were included in this study. After obtaining the informed consent, detailed clinical history was taken and thorough conventional oral examination (COE) was performed. The area of OPMDs was visualized by VELscope™ and the fluorescent visualization loss (FVL) was recorded. An incisional biopsy was performed at the FVL area for histopathological examination. VELscope™ results and histopathological results were compared and sensitivity and specificity were calculated. Mean age of the patients in this study were 37.54±12.78 and male to female ratio was 2:1. According to this study, sensitivity of VELscope™ was 94.4% and specificity was 23.8%. Positive predictive value was 68.0% and negative predictive value was 71.4%. Results of the study revealed that VELscope™ has an optimistic potential as a clinical auxiliary method in detecting OPMDs before performing a biopsy. This device may be an effective adjunct in community oral cancer screening when used with proper clinical judgment. This study suggests for future studies with two scenarios: first with larger sample size, for instance, population-based oral cancer screening and the second with hospital-based clinical studies with determination of marginal clearance using VELscope™.**

Key words; oral potentially malignant disorders, VELscope, autofluorescence

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Introduction

Oral malignancy and oral potentially malignant disorders (OPMDs) are major economic and clinical burden for the health care around the world (Ferlay *et al.*, 2013). Incidence of oral cancer; most common is oral squamous cell carcinoma (OSCC), is

still high in developing countries where the prevalence of key risk factors such as use of tobacco and alcohol remains high. Five-year survival rate of oral cancer varies from 81% for patients with localized disease to 42% for those with regional disease to 17% if distant metastases are present (Fedele *et al*., 2009). In Myanmar, oral cancer stands at the sixth position in males and the tenth position in females, contributing to 3.5% of all body cancers (Htun-Naing-Oo *et al*., 2011). Oral cancer (OSCC) often arises from OPMDs such as erythroplakia, leukoplakia, oral submucous fibrosis and oral lichen planus (Gaikwad *et al*., 2013).

Opportunistic screening of OSCCs and OPMDs by conventional oral examination (COE) at dental practices will identify the OPMDs and other mucosal disorders with similar clinical presentations. However, it is estimated that up to 15% of the general population have oral mucosal diseases at one time, but only very few have characteristics of OPMDs. Further, histological evidence of dysplasia and micro-invasive carcinoma has been found in clinically normal mucosa. Therefore, several chair-side adjunctive aids have been developed to help the practitioners with the aim of diagnosing high risk OPMDs from other oral mucosal lesions with similar clinical presentations (Scully *et al*., 2008).

VELscope^{TM} (Visually enhanced lesion scope, LED Medical Diagnostics Inc., Branabym, Canada) is based on the principles of tissue autofluorescence, generally recognized as a non-invasive, hand-held device designed to visualize early mucosal changes especially for OPMDs. The device emits the blue light between 400 and 460 nm wavelengths to excite fluorophores intrinsic in the oral mucosa. Within those excitation wavelengths, unaltered normal mucosa appears as a pale green autofluorescence which can be viewed through a selective, narrow band filter. Dysplastic tissue appears darker in color in comparison to surrounding healthy tissue because of alternative distribution pattern of tissue fluorophores and that is now recognized as fluorescent visualization loss (FVL) (Betz *et al*., 2002).

Several studies have been conducted on the efficacy of VELscope^{TM} on detection of OPMDs as well as oral malignant lesions with variable sensitivity and specificity value (Awan *et al*., 2011, Koch *et al*., 2011, Rana *et al*., 2012, Hanken *et al*., 2013, Sawan & Mashlah, 2015 and Ganga *et al*., 2017). In addition, it was said that routine VELscope use has been challenged because this particular device does not support all of the principles of evidence-based decision-making (Balevi, 2007). Regarding peer-reviewed VELscope studies, many have been performed on patients with known oral dysplasia or OSCC confirmed by biopsy. And several criticisms have been emphasized on this device because it needs to train dentists to use, thus this device has the limited capacity to use by general dentist (Laronde *et al*., 2007, Mascitti *et al*., 2018).

There was no previous study on the efficacy of autofluorescence devices used for detection of OPMDs in Myanmar. The results of this study will support in community-based survey on the early detection and screening of oral cancer and further improve the survival of oral cancer patients. Hence, the aim of this study was to evaluate the efficacy of the autofluorescence-based imaging system (VELscope^{TM}) in detection of OPMDs. To fulfill the main objectives, this study has also described the demographic features of OPMDs in Myanmar patients and further explored the association between the

findings of autofluorescence and histological examinations.

Materials and Methods

This study is an institutional and laboratory based cross-sectional descriptive study. Study population is a total of 57 OPMD patients collected by using convenient sampling method and sample size calculation was based on the study of Warren *et al*., (2007). Department of Oral Medicine and Department of Oral and Maxillofacial Surgery, University of Dental Medicine, Yangon were selected as study areas and study period was one year.

Data Collection Methods and Tools

Selection of the OPMD patients was based on the inclusion criteria. Patients with clinically diagnosed OPMDs were included in this study, recorded with oral mucosal assessment form and obtained informed consents for ethical consideration. Oral squamous cell carcinoma patients were also studied for positive control. Patients who deny to incisional biopsy and patients who are unfit for surgical procedures were excluded.

Conventional Oral Examination and Autofluorescence Examination

A total of 57 patients with a clinical diagnosis of OPMDs and OSCCs presenting to Department of Oral Medicine were screened and obtained the informed consent. Following history taking, the conventional oral examination (COE) was performed under incandescent light source and the data were recorded on the assessment form.

The principal site of morphologically altered tissue was photographed. Autofluorescence examination was performed using VELscope™ under the dimmed room light. The patient was requested to wear protective eye wear throughout the procedure. Autofluorescence examination was performed two times by two different operators from Department of Oral Medicine. The fluorescence visualization loss (FVL) seen as the dark area was marked and followed by incisional biopsy.

Histopathology Examination

Fluorescent visualization loss (FVL) areas of OPMDs were evaluated by incisional biopsy after autofluorescence imaging. For histopathological diagnosis, routine processing and paraffin embedding were performed on each incised soft tissue specimen. 4 µm thick sections were cut from each paraffin block and stained with haematoxylin and eosin. The slides were examined under a light microscope by two oral pathologists, and the results were blinded to each other. Epithelial dysplasia was assessed on architectural and cytological changes according to World Health Organization (WHO) Classification 2005 (Barnes *et al*., 2005).

Data Management and Analysis

Data entry and analysis were performed according to Statistical Package for Social Software (SPSS) version 20.0. Comparison of results of autofluorescence and histopathology were presented in a cross tabulation and agreement of the results were calculated using Kappa statistics. Sensitivity and specificity was calculated for statistical evaluation of the VELscope™ results comparing to incisional biopsy results as gold standard method. The true and false positives and negatives were applied on basic of Habib *et al*. (2015).

Sensitivity, specificity, positive predictive value and negative values were described with their 95% confidence interval. Differences and associations

between the autofluorescence test and dysplasia grade were examined using Chi square test with significance set at $p<0.05$. A receiver operating characteristic curve (ROC) was used to estimate the diagnostic value of the test.

Ethical Consideration

This study was approved by Research and Ethical Committee of University of Dental Medicine, Yangon. For ethical consideration, only the patients who gave an informed consent on their own wishes were included in the study. For the safety precaution, necessary preoperative blood investigations were performed and only the patients who were fit to undergo surgical procedures were studied. The expenses for preoperative blood investigations, incisional biopsy procedures and histopathologic diagnostic procedures were supported form external grant of Department of Medical Research, Ministry of Health and Sports, Myanmar. After the study procedures, appropriate treatment and referral for these patients were done in accordance with the histopathological diagnoses.

Results and Discussion

This study was conducted on 57 OPMD patients seeking treatment at Department of Oral Medicine, University of Dental Medicine, Yangon. In this study, male and female ratio was about 2:1 with a mean age of 37.54±12.78 (Figure 1). Interestingly, within the male patients with OPMDs, highest age group belongs to 21 to 30 year age group. This younger male predominance pointed out the accustomed smoking and betel quid chewing habit in younger generation in recent years. In olden days, betel chewing is accepted as traditionally habit among male population. There is an increased popularity of betel quid chewing habit and a huge blooming of betel quid market in many major cities of Myanmar, and because of that patients with OPMDs upraised highest frequency in today.

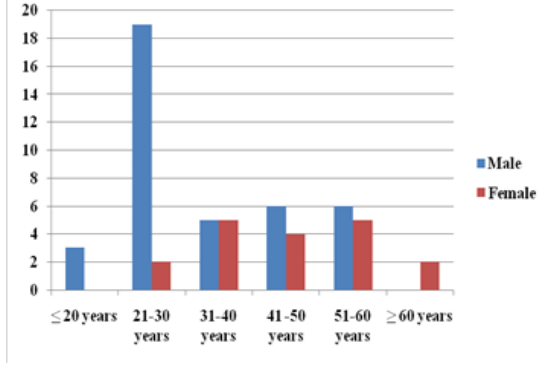

Figure 1. Age and sex distribution of the patient with OPMDs (n=57)

Out of 57 OPMD patients, majority of patients (63.2%) had oral submucous fibrosis followed by oral lichen planus (19.3%) and oral leukoplakia (8.8%) (Table 1). According to these findings, there was a higher proportion of oral submucous fibrosis patients which is mainly caused by betel quid chewing habit in this study reflects increased consumption and addiction of betel quids in Myanmar.

Table 1. Distribution of the clinical diagnosis of OPMD patients in the study

Clinical diagnosis of OPMDs	n (%)
Oral submucous fibrosis	36 (63.2)
Oral lichen planus	11 (19.3)
Leukoplakia	5 (8.8)
Lichenoid reaction	2 (3.5)
Erythroplakia	1 (1.8)
Chronic unhealed ulcer	2 (3.5)

Table 2. Comparison between the VELscope™ results and histopathological findings among the study populations (n=57)

VELscope™ Results	Histopathological Findings		Total
	Dysplasia Positive	Dysplasia Negative	
VELscope™ Positive	34	16	50
VELscope™ Negative	2	5	7
Total	36	21	57

(Sensitivity = 94.4%, Specificity = 23.8%, Positive predictive value = 68.0%, Negative predictive value = 71.4 %)

The sensitivity, specificity, positive predictive value and negative predictive value were calculated by comparing VELscope™ results and incisional biopsy results. Sensitivity of 94.4%, specificity of 23.8%, positive predictive value of 68.0% and negative predictive value of 71.4% were revealed (Table 2). Koch *et al*., (2011) showed a higher sensitivity (96.8%) and specificity of (95.8%) of VELscope™ to diagnose OSCC. Awan *et al*. (2011) evaluated 126 OPMD patients with VELscope™ and observed high sensitivity (84.1%) and low specificity (21.4%) using WHO criteria. Rana *et al*., (2012) showed that using the VELscope™ leads to higher sensitivity (100% versus 17%), but a lower specificity (74% versus 97%) as compared to COE. On the other hand, Hanken *et al*. (2013) examined 120 patients with suspicious oral lesions and found VELscope™ has a higher sensitivity (22.0%), and a lower specificity (8.4%). Sawan and Mashlah (2015) revealed low sensitivity (74.1%) and high specificity (96.3%) in the hospital-based study with the 748 Syrian populations.

In the present study, 16 cases show positive VELscope™ results although no sign of dysplasia was noted in histological examination. These false positive findings in the current study might be due to the inclusion of oral lichen planus, which is caused by chronic inflammatory auto-immune reaction rather than cellular changes. Two specimens were assessed as false negative. Histopathologically, aforementioned false negative cases were assessed as severe epithelial dysplasia although FVL was not apparent. These cases are clinically noted as erythroplakia and oral lichen planus, which are macroscopically suspected lesion area for high malignant transformation.

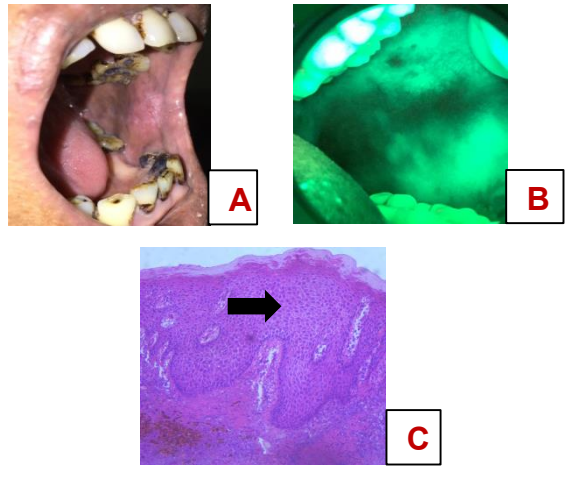

Figure 2. Clinical and histological pictures of oral leukoplakia
2-A. Oral leukoplakia
2-B. VELscope™ results on the lesion (Yellow arrow = abnormal mucosa with VFL: Visual fluorescence loss, Black arrow = normal mucosa)
2-C. Histopathological Results showing epithelial dysplasia (H&E stain x 100)

In the current study, all the OPMDs were firstly examined using VELscope™ and area of visualization fluorescence loss (VFL) were examined by incisional biopsy (Figure 2). This representative mucosal

biopsy of the oral cavity showed dysplastic squamous epithelium (Figure 2) and a high-grade epithelial dysplasia. In comparison, the dysplasia on epithelium showed a loss of maturation and nuclear atypia, high nuclear-to-cytoplasmic ratio and nuclear irregularity, involving the whole squamous cell layer of the mucosa. However, invasive tumour growth was not found.

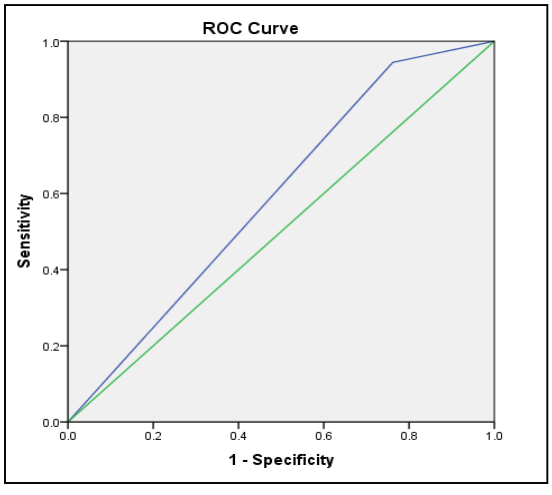

Figure 3. Receiver operating characteristic (ROC) curve for VELscope™ (AUC = 0.591, 95% CI: 0.432-0.751, *p*=0.254)

When sensitivity of VELscope™ examination was plotted against its specificity in ROC curve, the diagnostic value of VELscope™ was detected to be low (AUC=0.591, 95% CI: 0.432-0.751, *p*=0.254) (Figure 3). Results of this study pointed out that VELscope™ examination is a non-invasive procedure which provides a real-time result; it can be applied in patients who are contraindicated for biopsy due to several uncontrolled systemic diseases. However, due to several false positive results from FVL not only in dysplastic cases but also in inflammatory lesions demanded careful clinical judgment is essential for the proper use of VELscope™. It should be only be used in patients without clinically dangerous-looking lesion which are not indicated for biopsy and histopathological examination.

Conclusion

Findings from this study added to the growing evidence that supports the use of VELscope™ as adjunctive oral cancer screening device. However, a good clinical judgment and careful case selection are essential to detect early cancerous changes in OPMDs and high-risk lesions. To augment the efficacy of VELscope™ in early detection of oral cancer, it can be combined with vital tissue staining with toluidine blue. This device allows for a simple and cost-effective marginal determination in suspicious lesions during COE, monitoring oral lesions, and guiding the biopsy. It was found that the VELscope™ could not totally replace the gold standard, histopathology procedure. Therefore, this device may add sensitivity to the oral tissue examination and be an effective adjunct for high-risk patients. In addition, it could be applied in detection of field alterations in tumor margins of oral cancer patients during surgical procedures. Thus, this study further highlighted the diverse fields to perform as future researches; for community-based researches with larger sample size should be carried out to determine efficacy of VELscope™ in detection of OPMDs as well as for hospital-based clinical study to identify subclinical high-risk fields with cancerous and precancerous changes in oral cancer patients.

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The authors declare there is no potential conflict of interest.

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