

VELscope versus toluidine blue for detection of dysplastic changes in oral keratotic lesions: diagnostic accuracy study

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Background/aim

Various techniques have been implemented in the early detection of oral potentially malignant disorders including commonly occurring hyperkeratotic lesions. The objective of the present study was to assess the efficacy of visually enhanced lesion scope (VELscope Vx) versus toluidine blue (TB) with reference to histopathological examination in the detection of dysplastic changes in oral keratotic lesions.

Patients and methods

A total of 30 patients having oral keratotic lesions were clinically diagnosed and subjected to VELscope Vx and TB examination. Histopathological assessment of biopsied lesions was also done. Sensitivity, specificity, positive and negative predictive values were obtained for both VELscope and TB and were compared with histopathological examination.

Results

VELscope Vx was able to identify four out of seven cases with mild dysplasia and a case of oral squamous cell carcinoma, while TB was able to identify five cases and the oral squamous cell carcinoma case as true positive cases. Thus, sensitivity was 62.5 and 75% for VELscope Vx and TB, respectively. Regarding the specificity of VELscope Vx, it was 71.4% while TB had a specificity of 85.7%.

Conclusion

The sensitivity and specificity of TB examination outweighed those of VELscope Vx in detecting dysplastic changes within keratotic lesions.

Keywords:

cancer, dysplasia, keratosis, toluidine blue, VELscope Vx

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Introduction

Cancer is amongst the most frightful diseases the human race has been facing since decades [1]. Oral cancer positions itself as the sixth most commonly occurring cancer worldwide, where 500 000 new cases are discovered each year, representing roughly 3% of all malignancies [2].

The occurrence of oral malignancy has ascended in the past decade and is generally discovered when the lesion is symptomatic and at a late stage. In the past decades, the general 5-year survival rate for oral malignancy have stayed low at nearly 50%, thus ranking it among the worst cancer death rates. This has been related to the absence of experts that contribute to early recognition, detection, and diagnosis. Regardless of noteworthy advances in tumor treatment, early identification of abnormal oral changes remains the most ideal approach in guaranteeing better survival rates and enhanced personal satisfaction with improved quality of life [3].

Oral cancer can occur in the lips, tongue, buccal mucosa, and gingiva, and also in the floor of the mouth, palate, tonsils, and oropharynx. Oral squamous cell carcinoma (OSCC) can involve any tissue lined with oral mucosal epithelium and represents 96% of all oral malignancies [4,5]. Known etiological risk factors for OSCC include tobacco, betel quid, alcohol, and nutrients inadequacy; however, recent evidence puts human papillomavirus as a causative factor in malignancies of the base of the tongue, tonsils, and oropharynx in patients not having the conventional risk factors. OSCC is frequently preceded by visible and histological changes in the oral mucosa [6]. Conditions that can possibly turn into malignancies are referred to as oral potentially malignant disorders (OPMDs) and these incorporate leukoplakia, erythroplakia, oral submucous

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fibrosis, oral lichen planus (OLP), and actinic keratosis. The clinical appearance of OPMDs is an important predictor of malignant transformation. Although the erythematous or mixed white and red lesions have a higher rate of malignant transformation (14–50%) than the flat white lesions, these keratotic white lesions are more commonly encountered and could have a considerable risk of malignant transformation (4–18%). The way to enhance patient prognosis is through early identification, diagnosis, and management of these lesions [7].

The present protocol in diagnosing OPMDs is conventional oral examination (COE), which includes visual investigation of the oral cavity with tactile examination of head and neck lymph nodes by a medical or dental expert. However, harmful changes may still be overlooked by COE as dysplasia might be found in clinically normal looking mucosa. Moreover in many cases, COE cannot differentiate between benign and dysplastic changes because of the fact that various oral malignancies can appear similar to benign conditions [8].

Histopathological examination remains the gold standard for diagnosing dysplastic lesions. However, surgical blade biopsy is an invasive method and carries the burden of tumor seeding. It is done when the lesion shows either side effects or becomes symptomatic or clinically displays signs of malignancy [4].

Thus, different adjunctive and noninvasive techniques have been introduced to assess the oral conditions. One of those techniques is vital staining with toluidine blue (TB) and another is the visual representation techniques which have been proposed to enhance the quality of clinicians in screening any irregular tissue changes including OPMD and malignant lesions [8].

TB is the most generally and habitually adjunctive technique utilized to assess oral mucosal neoplastic disorders. TB is considered to be the most superiorly used technique in the detection of OSCC. TB is an essential thiazine metachromatic dye; its acidophilic properties are in charge of its affinity for nucleic acids. TB ties nuclear materials of tissues with high DNA and RNA contents. Positive lesions are stained in royal blue, while the negative ones take a light blue stain or do not stain at all [9].

The visually enhanced lesion scope system is a hand device that recognizes the loss of normal tissue

autofluorescence (AF) of dysplastic and neoplastic tissues by application of direct fluorescent light. The loss of fluorescence is the result of a progression of histological and biochemical modifications like the increase in nicotinamide adenine dinucleotide and the decrease in substantial flavin adenine dinucleotide, changes in collagen arrangement because of the breakdown of the extracellular matrix by dysplastic cells, and neoangiogenesis [10].

Visually enhanced lesion scope (VELscope Vx) consists of a source of light that emanates a wavelength of 400–460 nm and a manual part for direct visualization. Under this light, typical oral mucosa produces a green AF, whereas pathological areas ingest the fluorescent light and appear dark [11].

The aim of the study was to evaluate the efficacy of VELscope Vx versus TB in reference to histopathological examination in the detection of dysplastic changes in oral keratotic lesions.

Patients and methods

A total of 30 patients clinically diagnosed with oral keratotic lesions were recruited in this contemplate and the entire protocol procedures were explained at the beginning of the study for each patient and a written informed consent was obtained.

The study was carried out according to the ethical guidelines of the World Medical Association (Declaration of Helsinki) for studies involving human participants and the study protocol was approved by the Ethics Committee at the National Research Centre (NRC) with the registration code: 14-133.

Patients satisfying the study criteria underwent all the required protocol steps including history taking, clinical oral examination, VELscope Vx (LED Dental Inc., Vancouver, British Columbia, Canada) investigation, TB vital staining, and finally surgical biopsy of the lesion in the same visit. The inclusive criteria included patients 18 years old and over with oral keratotic lesions confirmed by COE. Patients already diagnosed with OSCC and those with medical conditions that contraindicate the surgical biopsy taking and those who did not sign the consent were not included.

Personal information, medical and social history including smoking habits and history of the lesion

occurrence were obtained from each patient. After history taking, thorough clinical examination of the entire oral mucosa including the suspicious lesion was performed under normal incandescent light. Following this comprehensive examination, clinical tentative diagnosis was established. The principal area (site) of morphologically altered mucosa was photographed. AF examination was performed using the VELscope Vx under dimmed room light, with protective eye wear worn by the patient throughout the procedure. The outcome of the AF examination was assessed according to the manufacturer's literature, that is, fluorescence visualization loss (FVL), fluorescence visualization retained (FVR), and photodocumentation of the lesion under AF was done.

TB staining was performed following the VELscope Vx examination. The steps of TB staining was first asking the patient to rinse the mouth with water for 20 s, then with 1% acetic acid for 20 s to remove any rosey saliva. Application of 1% TB solution for 20 s was done with a cotton swab. After that, the patients were asked to rinse again with 1% acetic acid for 20 s and finally with water to reduce the extent of mechanically retained stain. The lesion was then examined and photographed for recording and for interpreting the staining results. Lesions stained royal blue were considered positive, while lesions with pale blue or no stain, were considered negative [12].

Finally an incisional or excisional biopsy of the lesion was performed with a scalpel under local anesthesia for histopathological assessment. The selection of the biopsy site took into consideration any area of FVL identified by the VELscope Vx or area with retained TB stain within the lesion. Biopsy specimens were fixed in formalin and were sent for histopathological examination where they were blocked in paraffin, stained with hematoxylin and eosin. The presence of dysplasia was considered as 'positive' and absence of it was considered as 'negative'.

Statistical analysis

Data were collected and analyzed by IBM SPSS 20 (statistical package for social sciences; SPSS Inc., Chicago, Illinois, USA).

Sensitivity, specificity, and positive and negative predictive values were obtained for both TB and VELscope Vx according to Rethman *et al.* [4] as shown in Table 1.

Results

A total of 30 patients were eligible at the beginning of the study. Later on, one case refused to do the surgical biopsy after initial acceptance and undergoing all the other procedures. Patient's flow chart is demonstrated in Fig. 1.

From the 30 patients enrolled in this study, 22 (73.3%) were males and eight (26.6%) were females. Four (13.3%) patients only were less than 20 years old and two (6.6%) were older than 70 years. The rest

Table 1 Definitions of diagnostic accuracy measures used in the study

Sensitivity	The proportion of people who test positive for a specific disease among a group of people who have the disease
Specificity	The proportion of people who test negative for a specific disease among a group of people who do not have the disease
Positive predictive value	The proportion of people in a specified population with positive test results who have the disease
Negative predictive value	The proportion of people in a specified population with negative test results who are disease free

Figure 1

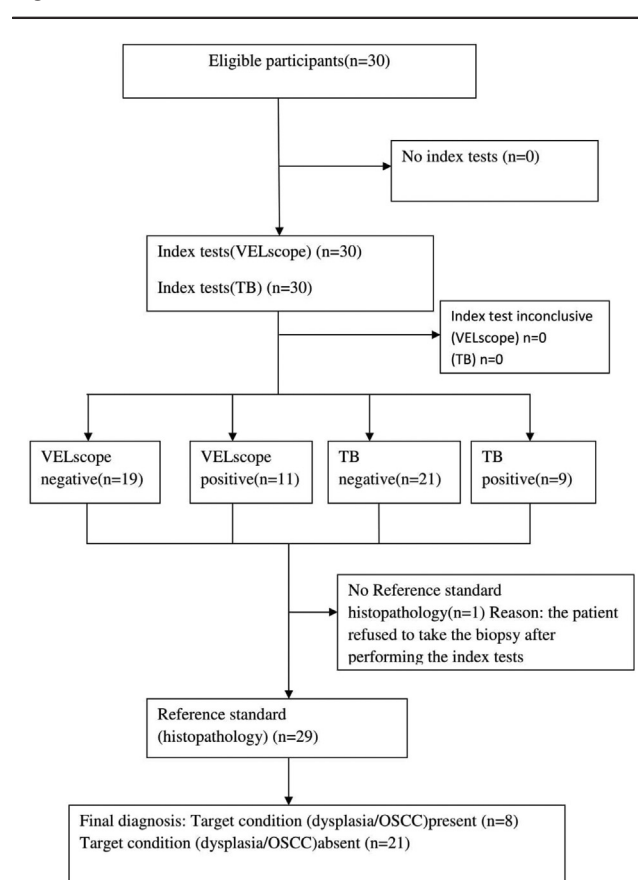


Chart reporting the flow of the participants during the study. OSCC, oral squamous cell carcinoma; TB, toluidine blue; VELscope, visually enhanced lesion scope.

of the patients were divided equally between the two age groups of 30–50 and 50–70 years old (12 patients in each group). Regarding smoking habit, 16 (53.4%) patients were smokers; 10 (33.3%) patients were nonsmokers, whereas four (13.3%) patients were former smokers. Demographic data and examination results of each patient are presented in Table 2.

Clinical results

The lesions encountered in this study were 20 cases of leukoplakia, four cases of OLP, two cases of chronic hyperplastic candidiasis (CHC), two cases of verrucous hyperplasia, one case of frictional keratosis, and one case of alveolar ridge keratosis. The buccal mucosa was the most common site of these lesions in all 20 cases. Other intraoral sites were the tongue in four cases, the palate in two cases, the retromolar area in two cases, the gingiva in one case, and the alveolar ridge mucosa in one case.

Histopathological results

Regarding the histopathological distribution of the lesions, there was one case missing, where

the patient refused to take the biopsy after initial acceptance. The remaining 29 cases were diagnosed as 21 cases of hyperplastic and hyperkeratotic stratified squamous epithelium without dysplasia, seven cases with mild dysplasia, and one case of OSCC.

Visually enhanced lesion scope Vx results

From the 29 cases with available histopathological results and after excluding the case without histopathology in which the VELscope Vx test was negative, there were 11 cases which showed FVL, that is, positive through VELscope Vx examination and 18 cases displaying normal pale green image indicating FVR, that is, negative. From the 11 positive cases showing loss of fluorescence with the VELscope Vx, four cases were found to have mild dysplasia and one case diagnosed as OSCC by histopathology, that is, true positive, while the other six cases were nondysplastic, and therefore considered as false positive. On the other hand, the 18 cases with negative results were divided into 15 true negative

Table 2 Demographic data and results of each patient participated in the study

No.	Age	Sex	Clinical diagnosis	TB	VELscope	Histopathological examination	Smoking habit
1	52	Male	Homogeneous leukoplakia	Negative	Negative	Missing result	Former smoker
2	60	Male	Leukoplakia	Negative	Negative	Nondysplastic	Former smoker
3	55	Male	OLP	Negative	Negative	Nondysplastic	Current smoker
4	38	Male	CHC	Negative	Negative	Nondysplastic	Current smoker
5	24	Male	Speckled leukoplakia	Positive	Positive	OSCC	Nonsmoker
6	47	Male	Leukoplakia	Negative	Negative	Nondysplastic	Current smoker
7	46	Female	Leukoplakia	Positive	Positive	Nondysplastic	Nonsmoker
8	63	Male	Leukoplakia	Negative	Negative	Nondysplastic	Former smoker
9	62	Male	Leukoplakia	Negative	Negative	Nondysplastic	Former smoker
10	68	Male	Leukoplakia	Negative	Negative	Nondysplastic	Current smoker
11	42	Male	Leukoplakia	Negative	Negative	Nondysplastic	Current smoker
12	65	Male	Verrucous leukoplakia	Positive	Negative	Mild dysplasia	Current smoker
13	70	Female	Thin leukoplakia	Negative	Positive	Mild dysplasia	Nonsmoker
14	66	Male	Speckled leukoplakia	Positive	Positive	Mild dysplasia	Current smoker
15	47	Male	CHC	Negative	Positive	Nondysplastic	Current smoker
16	27	Female	OLP	Negative	Negative	Nondysplastic	Nonsmoker
17	41	Female	Alveolar ridge keratosis	Negative	Positive	Nondysplastic	Nonsmoker
18	49	Male	Frictional keratosis	Negative	Negative	Nondysplastic	Current smoker
19	47	Female	Leukoplakia	Negative	Negative	Nondysplastic	Nonsmoker
20	72	Female	Leukoplakia	Positive	Negative	Nondysplastic	Nonsmoker
21	56	Female	Leukoplakia	Negative	Positive	Nondysplastic	Current smoker
22	60	Male	Leukoplakia	Positive	Positive	Mild dysplasia	Current smoker
23	54	Female	Leukoplakia	Positive	Negative	Mild dysplasia	Nonsmoker
24	30	Male	Homogeneous leukoplakia	Negative	Negative	Nondysplastic	Current smoker
25	19	Male	Oral verrucous hyperplasia	Positive	Negative	Mild dysplasia	Current smoker
26	37	Male	OLP	Negative	Positive	Nondysplastic	Nonsmoker
27	57	Male	OLP	Positive	Positive	Nondysplastic	Nonsmoker
28	27	Male	Oral verrucous hyperplasia	Negative	Negative	Nondysplastic	Current smoker
29	41	Male	Homogeneous leukoplakia	Negative	Negative	Nondysplastic	Current smoker
30	42	Male	Speckled leukoplakia	Negative	Positive	Mild dysplasia	Current smoker

CHC, chronic hyperplastic candidiasis; OLP, oral lichen planus; OSCC, oral squamous cell carcinoma; VELscope, visually enhanced lesion scope.

cases which were found to be nondysplastic on histopathological examination and three false negative cases (they showed mild dysplasia on histopathological examination).

VELscope Vx sensitivity and specificity were 62.5 and 71.4%, respectively, as shown in Table 3. Positive and negative predictive values were 45.5 and 83.3%, respectively.

Toluidine blue results

From the 29 cases with available histopathological results and after excluding the case without histopathology in which the TB test was negative, nine cases were stained royal blue and the lesion retained the dye, that is, positive while 20 cases failed to retain the dye and the lesion was considered negative. From the nine positive cases, five cases were found to have mild dysplasia and a case diagnosed as OSCC by histopathology, that is, true positive, whereas the other three cases were nondysplastic, and therefore considered as false positive. On the other hand, the 20 cases with negative results were divided into two false negative cases (histopathological examination showed mild dysplasia) and 18 true negative cases which were found to be nondysplastic on histopathological examination.

Sensitivity and specificity of TB staining were 75 and 85.7%, respectively. Positive and negative predictive values were 66.6 and 90%, respectively, as shown in Table 4.

Figure 2 shows a case of OSCC where both VELscope Vx and TB were positive whereas Fig. 3 shows a case of verrucous leukoplakia where TB gave positive and VELscope showed negative results.

Table 3 Cross-tabulation between visually enhanced lesion scope and histopathological results

	Histopathology		Total
	Positive	Negative	
VELscope			
Positive			
Count	5	6	11
% within histopathology	62.5	28.5	37.9
Negative			
Count	3	15	18
% within histopathology	37.5	71.4	62.1
Total			
Count	8	21	29
% within histopathology	100.0	100.0	100.0

VELscope, visually enhanced lesion scope.

Discussion

OSCC can emerge *de novo* or is mostly preceded by OPMDs. Many of these OPMDs start as a reversible step of hyperkeratosis, where the epithelium thickness increases and an excess of keratin is observed on its outer layer. Later, other morphological changes as the different stages of dysplasia occur. Keratotic lesions can mask deeper lying changes, which may range from simple hyperplasia to invasive cancer [13].

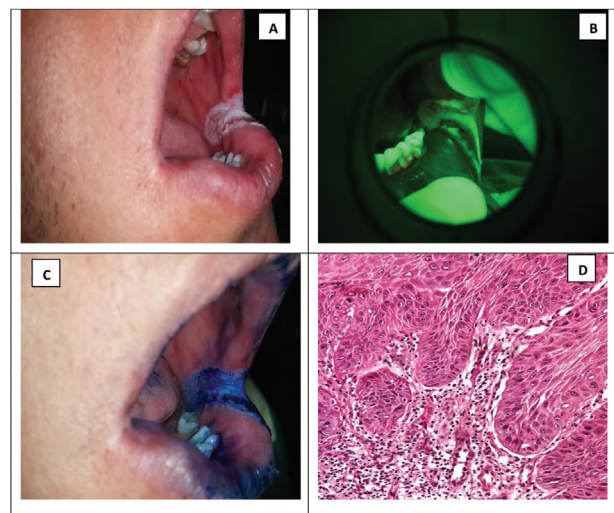
Leukoplakia is the most common potentially malignant disorder which was the case in our study

Table 4 Cross-tabulation between toluidine blue and histopathological results

	Histopathology		Total
	Positive	Negative	
TB			
Positive			
Count	6	3	9
% within histopathology	75.0	14.3	31
Negative			
Count	2	18	20
% within histopathology	25.0	85.7	69
Total			
Count	8	21	29
% within histopathology	100.0	100.0	100.0

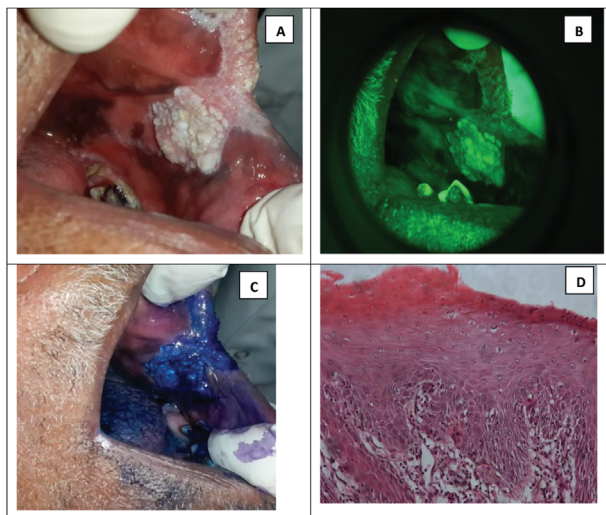
TB, toluidine blue.

Figure 2



(a) A case of oral squamous cell carcinoma clinically presenting in the form of speckled leukoplakia; (b) visually enhanced lesion scope examination showing loss of fluorescence, that is, positive result; (c) toluidine blue staining of the lesion showing retention of the stain, that is, positive result; (d) hematoxylin and eosin stained section of the same case showing hyperplastic and hyperkeratotic stratified squamous epithelium with signs of malignancy and rupture of basement membrane detected in some areas. Epithelial masses showed hyperchromatism and abnormal mitotic figures. The underlying connective tissue shows intense inflammatory cell infiltrate.

Figure 3



(a) A case of verrucous leukoplakia with mild dysplasia; (b) visually enhanced lesion scope examination of the case showing no loss of fluorescence; (c) toluidine blue staining of the same lesion showing royal blue stain, that is, true positive; (d) hematoxylin and eosin stained section of the same case showing hyperplastic and hyperkeratotic stratified squamous epithelium with mild dysplastic features as abnormal mitotic figures and hyperchromatism detected in the basilar part of the epithelium.

where 20 out of the 30 cases were leukoplakias. The reported annual malignant transformation of leukoplakia into OSCC is ~1–2%. Several factors in patients with leukoplakia are suggested to predict the increased risk of malignant transformation such as age, sex, tobacco habits, the homogeneity, size, and site of the lesion within the oral cavity as well as the degree of epithelial dysplasia, if present [14].

Other keratotic lesions like OLP, CHC, and frictional keratosis are commonly encountered during routine dental examination. Apart from frictional keratosis, which has not been reported to show dysplastic changes, OLP and CHC may show variant degrees of dysplasia and malignant transformation which is more likely to occur in patients with the erosive type of OLP. It has been accepted that thorough mucosal examination should be a part of routine dental examination in order to detect oral cancer and dysplastic lesions. COE has been shown to be a reliable method and is the currently accepted practice for the detection of oral cancer and OPMD. Detection of lesions may be enhanced by the use of adjunctive diagnostic aids such as oral CDx, TB, ViziLite, or VELscope. Research is continuing into the effectiveness of these and other aids; however, as yet there is insufficient evidence to justify their use as screening adjuncts [15].

In this study, we assessed the accuracy of two of these adjunctive diagnostic aids which are the VELscope Vx and TB in detecting dysplastic changes within oral keratotic lesions. Both tests were performed in the same visit for all the participants in the study after history taking and thorough clinical examination. Then, a double wedge biopsy was taken from the lesion for histopathological examination as it is considered the gold standard in detection and grading of dysplasia and malignant transformation [16]. Statistical analysis included the calculation of sensitivity, specificity, and positive and negative predictive values for both tests.

In this study, it was found that eight out of the 29 (27.5%) cases with available histopathological results had dysplastic changes with one of the eight cases being OSCC. This case was in a young 24-year-old man with no reported risk factors as smoking or drinking alcohol. The increased incidence of oral cancer among young adults without any known risk factors was reported in a study in which 44 cases younger than 40 years old out of 606 cases of OSCC were encountered [17].

In a previous review, the authors stated that many of the young individuals (<45 years old) presenting with OSCC in the studies included in their review have declared that they never have smoked or consumed alcohol excessively. They also mentioned that the exposure of these individuals to carcinogens such as alcohol and tobacco is too short to induce malignant transformation in those younger patients. Hence, it was suggested that the poor survival rate of young patients with stage II disease, with no history of exposure to tobacco, is due to an inherited predisposition to chromosomal abnormalities which may have led to a more rapid disease progression [18].

Regarding the smoking habit, 16 out of the 30 cases included in our study were current smokers; four cases were former smokers while 10 cases were nonsmokers. Of the 16 current smokers, five of them developed mild dysplastic lesions in the oral cavity. Tobacco exposure through smoking is a well-established risk factor for oral cancer [19].

To the best of authors' knowledge, one study compared TB with VELscope in differentiating dysplastic and neoplastic lesions from benign lesions. In this study, the authors decided to suggest two scenarios where in the first scenario, lesions showing mild dysplasia on histopathology were considered positive, whereas in the second scenario, these cases were considered negative. They found that the sensitivity and

specificity of VELscope in the first scenario were 70 and 57.7%, respectively, whereas TB showed a sensitivity and specificity of 80 and 61.5%. In the second scenario, the sensitivity increased for both techniques (VELscope 76.5% and TB 88.2%), whereas the specificity declined to 51.3% for both [20].

The false positive cases of VELscope Vx and TB can be attributed to the presence of inflammation such as in the case of OLP. Moreover leukoplakias with rough surfaces can cause mechanical retention of TB stain resulting in false positive results.

The relatively lower sensitivity of VELscope Vx to dysplastic changes in keratotic lesions in our study could be explained by increased fluorescence of the superficial keratin layer masking the underlying dysplastic changes. This keratin was found to produce strong, collagen-like fluorescence [21]. Another explanation is that angiogenesis absorbs the fluorescent light and gives a dark image. Angiogenesis is generally associated with severe dysplasia or carcinoma *in situ*, as well as invasive disease, and is absent in healthy oral epithelium, mild, and moderate dysplasia [22].

In a study conducted to evaluate the benefit of direct visual fluorescent examination in screening potentially malignant mucosal lesions in a general population of patients presenting for dental care, the authors noted that some inflammatory conditions (traumatic ulcers, geographic tongue, inflammatory papillary hyperplasia, and chronic mucositis), physiologic features (melanin pigmentation and lymphoid aggregates), and certain anatomic sites (attached gingiva, tonsillar pillars, and floor of the mouth) showed loss of fluorescence upon examination with VELscope. As a result, they concluded that the use of VELscope does not add to the COE in routine screening for OPMD [23].

Regarding sensitivity of the VELscope Vx, our results were contradictory to Moro *et al.* [24] who found that the sensitivity of autofluorescence examination was 100% and to Rana *et al.* [25] who found that the use of VELscope increased the sensitivity from 17 to 100% compared with COE alone in detecting malignant lesions of the oral mucosa. Regarding specificity, Rana *et al.* [25] found that 64.23% of all examined lesions showed a loss of fluorescence, whereas only 4.88% of the lesions could be identified as dysplasia which could lead to overdiagnosis if the VELscope is used by a nonspecialist. Thus, they concluded that VELscope is very subjective, and both clinical experience and training are needed to accomplish good testing.

A conclusion from a previous study by Scheer *et al.* [26] stated that the results of VELscope examinations depend mainly on the experience of the examiner as the difference between loss of fluorescence and decreased fluorescence is arbitrary. They also pointed that although the sensitivity of the VELscope in their study was 100%, their patients were of a high risk group for oral cancer with 20 of the 64 patients included in their study having previous history of oral cancer.

Regarding TB, a meta-analysis assessing its effectiveness in identifying OSCC showed sensitivity ranging from 93.5 to 97.8% and specificity from 73.3 to 92.9% [27]. This is consistent with our results showing the decreased number of false negative results.

A former study demonstrated that the use of TB after COE raised the sensitivity from 53% (when using only COE) to 96.2% when COE was combined with TB examination, whereas the specificity decreased slightly from 80 to 77.5% [28]. Another research found the sensitivity for TB staining to be 95% and the specificity 71.45% [29]. On the other hand, a recent investigation stated that TB has higher sensitivity and specificity for malignant lesions than OPMDs where results demonstrated that the sensitivity of TB screening for malignant lesions was 92% and the specificity was 82%, whereas the TB sensitivity and specificity in detecting OPMDs were 61 and 80%, respectively [30].

Conclusion

From the results of our study, it can be concluded that TB is more efficient in detecting dysplastic changes within keratotic lesions than VELscope Vx. However, histopathological examination remains the gold standard technique in differentiating between benign, dysplastic, and malignant lesions. Limitation of our study is the small sample size and that is why future comparative studies with a larger sample size are recommended.

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Nil.

Conflicts of interests

There are no conflicts of interest.

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