Efficacy of Chemiluminescence (ViziLite™) as a Screening Method in the Detection of Clinically Suspicious Oral Cancerous and Precancerous Lesions

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Abstract: Several screening techniques based on light interaction with tissue have been described to aid clinicians in the detection of early oral cancerous lesions. One of the most studied techniques is chemiluminescence. This method has been used in different studies but always by Oral Medicine specialists.

Objective: To evaluate the chemiluminescence system as a screening method in the detection of clinically suspicious cancerous and precancerous oral lesions when used by clinicians without an Oral Medicine Speciality.

Study Design: A total of 100 patients attending the Oral Medicine Unit at the Dental School of the University of Seville were enrolled. All patients were current smokers and were above the age of 40. The clinical examination was performed by dental students who were instructed in the location and recognition of potentially malignant oral disorders, using visual examination and the chemiluminescence test ViziLite Plus ™ (Zila Pharmaceuticals, Phoenix, AZ, USA). To assess the validity of the chemiluminescence test as a screening method, a visual exam was performed by a specialist in Oral Medicine which was used as a *gold-standard*.

Results: Conventional oral visual examination by the Oral Medicine Specialist found 13 lesions suspicious for malignancy, out of which 7 were also detected using the chemiluminescence test. Furthermore, 87 patients were diagnosed as lesion-free, of which 49 obtained negative results during the chemiluminescence test and 38 patients had some sort of lesion. With these results, the test yielded a sensitivity of 0.56 and a specificity of 0.56. These results indicate values similar to other studies, in fact lower sensitivity values, possibly due to the lack of experience of the clinician.

Conclusions: The chemiluminescence test (ViziLite Plus™) did not present any advantages in terms of cost-benefit compared to conventional examination as a screening method for cancerous and precancerous oral lesions.

Keywords: Chemiluminescence, screening method, oral cancer.

INTRODUCTION

Currently, an estimated 643,000 new cases of head and neck cancers appear per year worldwide; 40% of these new cases are diagnosed as oral squamous cell carcinomas (OSCC) [1]. 60% of the malignant tumours diagnosed within the oral cavity are stage III or IV, when the tumour has already become symptomatic and has invaded neighbour structures or developed metastasis [2], increasing the mortality and morbidity rates. It is believed that a vast majority of OSCC derives from pre-malignant lesions [3] and the identification of these high risk lesions can be vital in controlling the disease [3] and to pinpoint possible changes in the mucosa [4].

Screening can be defined as the "application of a test to apparently healthy or disease-free individuals to detect those who probably have the disease and those that probably do not have the disease" [5]; an important aspect to consider regarding the screening method is that it was performed on symptom-free patients.

A general population screening does not assure a significant reduction in cancer mortality [6], although the latest figures [7-10] indicate that screening high risk individuals, as well as those with toxic habits such as alcohol and tobacco [11], patients over 40 years-old, and/or with a history of oral cancerous or precancerous lesions, would reduce the mortality and morbidity rate of the disease.

The International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) have calculated that millions of deaths could be avoided if efficient screening strategies for the disease were

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planned and implemented [12]. The most recommended strategy would be: firstly, to raise awareness regarding the importance of periodical check-ups; and secondly, the use of different aid systems to detect small cancerous and pre-cancerous lesions.

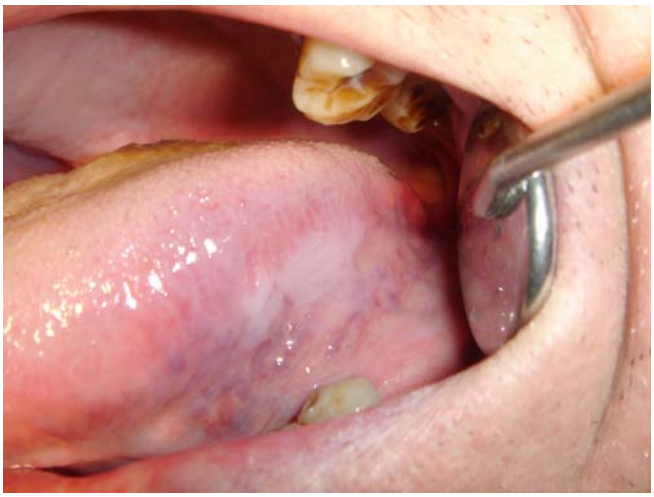

Figure 1: Conventional Visual Examination of a lesion.

Currently the most popular screening method for cancerous and pre-cancerous lesions is conventional visual examination of oral soft tissues in the dental practice (CVE) [2, 13, 14].

Conventional visual examination (CVE) has been very successful as a screening technique in areas of easy access such as skin [15], but in the oral cavity we come across several features which increase the limitations of finding and diagnosing oral cancer [16, 17]. In view of these limitations, new detection devices are constantly being ideated to aid health professionals to detect malignant and premalignant lesions. One of the methods that have drawn more attention in recent years has been the chemiluminescence technique and light-based tissue interactions.

This technique is based on the tissue reaction to a specific light form, and is performed in a manner similar to the method used to detect early cervix and uterus cancer called *Speculoscopy,* which has demonstrated negative predictive values of 94.7-99% [18]. This system focuses on using a blue-white chemical light which is absorbed by cells with normal tissue and reflected by cells with abnormal nucleus in neoplastic and dysplastic tissues.

The generated light is produced by two chemical compounds that come into contact once the vial is broken, triggering a chemical reaction that produces a light emission. Before being exposed to light, the tissues must be dehydrated and cleaned. A solution of 1% acetic acid is applied during a certain time frame to eliminate any possible epithelial residues. This solution also temporarily destroys the mucosal glycoprotein barrier and induces a cytoplasmatic dehydration allowing the light to penetrate and produce refractory changes within the tissues [19]. After the application of the dehydration solution and under the chemiluminescence light, the tissues containing cells with an altered nucleus-cytoplasm ratio, hyperkeratinized or with inflammatory modifications will present with an “acetic-white” aspect, as the dehydrated-white aspect would be described, and appear more opaque than normal. It is an easy, non-invasive technique that is well accepted by the patients and has no side effects [20].

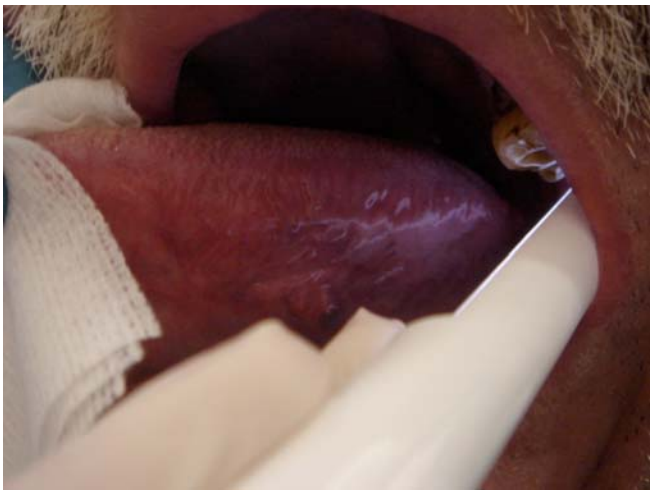

Figure 2: Light emission of a lesion using the chemiluminescence system.

Vizilite Plus™ (Zila Pharmaceuticals, Phoenix, AZ, USA) is the only commercially available chemiluminescence system approved by the United States Food and Drug Administration (U.S.F.D.A) to detect cancerous lesions [21] and has scientific evidence with no conflict of interest [19, 20, 22-28].

The main objective of this study was to evaluate the efficacy of the chemiluminescence (Vizilite Plus™ System) as a screening method when used by general dental practitioners and its application in patients with a high risk of suffering oral cancer

MATERIAL AND METHODS

One hundred patients (sample size calculated for α risk=0,025 with a sensibility level for the test of 15%) from the Dental School of the University of Seville were

enrolled in the study. A visual examination of the soft tissues of the oral cavity was performed on each patient. An examination with the Vizilite Plus™ System was also performed on each patient.

The inclusion criterion was: patients being seen in the Oral Medicine Department of the Dental School of the University of Seville who were smokers (more than 10 cigarettes per day and for more than 10 years), and had not complained of any lesions or symptoms in the oral cavity, and had understood and signed the informed consent form.

The examinations were performed by fifty (50) undergraduate dental students instructed in the location and recognition of potentially malignant lesions and also by an Oral Medicine Specialist. The main objective of these examinations was to discover clinical lesions in the oral mucosa suspicious of cancerous or precancerous oral cancer, including: homogenous and non-homogenous leukoplakias (not corresponding to hyperkeratosis of edentulous rigdes), erythroleucoplakias, ulcerated lesions without a traumatic history or with more than 15 days of evolution, and we also included lesions which could be classified as atrophic/erosive lesions and all the lesions that clinically could correspond to these variations.

Firstly, the undergraduate dental student performed a conventional tissue examination using an examination probe, a dental mirror and a sterile gauze (each student performed 2 conventional examinations and 2 exams with the chemiluminescence device). Following the visual exam, the dental student proceeded to use the Vizilite Plus™ System. This test is based on a solution of 1% acetic acid (glycol propylene + alcohol + sodium benzoate + 1% acetic acid + raspberry flavouring) and a light-based chemiluminescence system (hydrogen peroxide + acetylsalicylic acid) that produces a light with a 430 to 580 nm wave length during 10 minutes.

The Vizilite System recommended protocol is: the patient should rinse for 30 seconds using the 1% acetic acid solution. After rinsing, the chemiluminescence device is activated and the patients' oral mucosa is thoroughly examined. This exam is recommended without the dental chair light and with lights switched off in the room. If any "white-acetic" lesions are found, they will be considered as positive to the Vizilite System. The Oral Medicine Specialist subsequently performed the same examination, and these findings were defined as the gold-standard or the reference value. This reference value is termed as the *soft-gold-standard*, which is not as exact as a tissue biopsy, but is the accepted reference value in screening methods, given that it is not considered appropriate or ethically correct to biopsy negative areas [2, 29].

The findings from the light-based system performed by the student were then compared to the Oral Medicine Specialist's findings

We evaluated if the Vizilite Plus™ System can enhance the ability of undergraduate dental students to locate and recognize cancerous or precancerous lesions compared to the Oral Medicine Specialist.

For this purpose we analyzed the sensitivity, specificity, the positive predictive value (PPV) and the negative predictive value (NPV) of the system. The Kappa test was used to observe variations between the inter-examiner concordance coefficient when both screening methods were used. The exam duration of both methods was also measured.

All of the lesions considered as suspicious by the Oral Medicine Specialist were biopsied with a cold scalpel for subsequent anatomo-pathologic study. These results were not the end-purpose of this study, due to the fact we are testing the ability of using the chemiluminescence device as a screening method and not as a diagnostic tool.

The study was approved by the Ethical Committee of the University of Seville and all patients were given verbal and written informed consent forms.

RESULTS

Of the hundred [100] patients included in the study, forty three [43] were female and fifty seven [57] were male, with the average age being 51.4 years. The average tobacco consumption was 17.89 cigarettes per day and 85% of the patients had been smoking for more than 20 years.

The Oral Medicine Specialist found 13 suspicious lesions in the same number of patients; all lesions were white and could not be removed by scrapping. Only 7 of these lesions were identified by Dental Students using the chemiluminescence system. Only 1 lesion was identified by the light-based system that was not identified by clinical visual examination (CVE). 87 patients were described as lesion-free by the Oral Medicine Specialist, 49 of which proved to be lesion-free according to the chemiluminescence system used

Table 1: Results of the Chemiluminescence System. *With the Disease* is Defined when the Oral Medicine Specialist Considers a Lesion as Suspicious. PPV→ Positive Predictive Value. NPV→ Negative Predictive Value

Test results	With the disease	Without the disease
(+)	a=7	c=38
(-)	c=6	d=49
Sensitivity=a/a+c→7/(6+7)=**0.53**	**PPV**=a/(a+b)→7/(7+38)=**0.15**	
Specificity=d/(d+b)→49/(49+38)=**0.56**	**NPV**=d/(d+c)→49/(49+6)=**0.89**	

by the dental students, while 38 tested positive to the light-based test.

In view of these results, the sensitivity test as a screening method for precancerous or cancerous lesions was 0.53. The specificity was 0.57. The positive predictive value amounted to 0.15 and the negative predictive value was 0.89 (Table **1**).

According to the inter-examiner concordance coefficient (Kappa coefficient - κ), the chemiluminescence system made it decrease. When a clinical visual examination (CVE) performed by an undergraduate dental student was compared to the CVE carried out by an Oral Medicine Specialist, the concordance coefficient amounted to 0.1746, whilst the comparison of the CVE by an Oral Medicine Specialist and the chemiluminescence system used by a dental student amounted to 0.049. This decrease did not vary the Landys-Koch [30] scale regarding the strength of inter-examiner concordance since concordance was mild in both comparisons.

DISCUSSION

Firstly, we will outline the differences between a diagnostic test and a screening method. Screening techniques are applied to a patient that is free from a given disease to detect or diagnose pathology, whilst diagnostic tests (case findings) are those methods applied to a patient with established signs and symptoms (localised lesions). The main objective of the diagnostic test is to establish a definitive diagnosis and to apply the consequent treatment.

In recent times, the diagnostic gold standard test used to detect precancerous or cancerous lesions has been a soft tissue biopsy and an anatomo-pathology exam by a specialist. Nevertheless, the gold standard for screening methods is the qualified expertise opinion by an Oral Medicine Specialist or a Maxilo-facial Specialist, which is considered the gold standard or reference value.

Tissue biopsy would not be an acceptable gold standard for a screening method given that it would not be viable to take tissue samples from all the study patients due to the high number of cases in the screening test and the amount of patients without lesions at the time of the study.

One of the greatest mistakes is to confuse both concepts, and to compare screening methods with diagnostic tests [2]. This comparison has provided poor results due to the fact that screening methods were not created for this purpose.

In this study we have attempted to evaluate the benefits of using an oral mucosa localization system as a screening method, and not as a diagnostic tool. Consequently, the reference value of choice was the opinion of an Oral Medicine Specialist, not a tissue biopsy or an anatomo-pathology exam.

The predictive value of the chemiluminescence system as a screening method to detect suspicious cancerous and precancerous lesions reported similar results in our study compared to others when used as a diagnostic tool [19, 20, 23, 24]. It is important to note that previous studies evaluating the chemiluminescence system were not able to determine the sensitivity, specificity, PPV and NPV [22, 25, 26] as they did not have a gold standard as a reference. The previous studies were performed by an Oral Medicine Specialist using the light-based system, without using the specialist's opinion as a reference value for comparison.

Consequently, our study design is based on using a reference value to compare the efficacy of the chemiluminescence system when used in conditions similar to the daily clinical practice.

In the studies that used the chemiluminescence test as a screening method, the authors concluded that the system was highly sensitive but poorly specific. The same can be said in the cases when the system was

used as a diagnostic tool (when a lesion is present and an anatomo-pathology exam was used as a gold standard). All studies [19, 20, 23, 24, 28] bar one [27] concluded that the light-based system had poor specificity values with high sensitivity values.

Our study suggests that apart from poor specificity values, poor acceptable sensitivity values resulted when used as a screening method, probably due to the fact the observers were undergraduate dental students who are trained in locating suspicious lesions but do not have experience in daily clinical practice.

In terms of the inter-examiner concordance coefficient, the value decreased when the students used the light-based system, due to the high number of false positives accounted for in the test, although it did not vary on the strength of concordance quality scale showing low concordance between undergraduate dental student and Oral Medicine Specialist. This low concordance accounts for the need to look for new devices to aid general dentists in the art of locating and diagnosing potentially malignant lesions in routine daily oral examinations. It is important to bear in mind that the first line of screening are general practitioners, hence the need for screening and diagnostic tools that can enhance their examination diagnosis of precancerous and cancerous lesions compared to the opinion of an Oral Medicine Specialist [2].

The Vizilite Plus™ System did not help in this regard, in fact it increased the examiners doubts regarding non-suspicious lesions or in cases considered as normal variations.

It also produces much lower sensitivity and specificity values than CVE, which are estimated at 74-85% and 75-99% respectively [14].

It is also important to consider that 5-15% of the population have oral mucosa abnormalities that can be mistaken with cancerous lesions [16] and that dysplastic areas or “in situ” carcinomas can be present with clinically normal appearance [17], therefore this diagnosis must be done by a wide spectrum of oral health clinicians such as dental hygienists, general dentists and Oral Medicine Specialists. For these reasons, a test created to identify lesions in the oral cavity should report higher values, especially in terms of sensitivity, to justify the use and cost of the system.

CONCLUSIONS

The use of the chemiluminescence system as a screening method did not reveal benefits compared to CVE and does not help clinicians without an Oral Medicine Speciality to identify suspicious lesions which would be diagnosed by an Oral Medicine Specialist as potentially malignant.

More studies are called for, especially studies including more highly experienced dental practitioners and a larger sample size in order to extrapolate the experience to daily practice.

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