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Systematic Review

VELscope -Tissue fluorescence based diagnostic aid in oral precancer and cancer

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ABSTRACT

Oral cancer is one of the most dreaded disease associated with high morbidity and mortality. Being detected in later stages, most often it is associated with poor survival rate. Early diagnosis is very crucial and there have been numerous diagnostic adjuncts available to aid in its early diagnosis. VELscope is a new advanced optical technique which is appealed to detect the precancer and cancer lesions in its early stage. This article evaluates the VELscope technology in context to oral precancer and cancer.

Keywords: Oral cancer; precancer; diagnosis; optical; fluorescence; VELscope

1 INTRODUCTION

Early diagnosis is the most significant factor that can reduce the high mortality and morbidity associated with oral precancer and cancer. Presently, visual examination is the most common method used in the initial diagnosis.However, it cannot identify innocuous lesions and lesions that exhibit early cancerous changes.[1,2] There have been tremendous researches to advent new technologies to aid in early detection of cancer. Use of tissue fluorescence to detect the alterations associated with the oral cancer in the form of morphology and at molecular level is in the recent front.[1,2] The use of autofluorescence as a diagnostic tool for cancer detection was first time described as early as in 1924 and since then it is been intensely researched.[2,3] The use of tissue autofluorescence in the screening and diagnosis of precancerous lesions in the lung, uterine cervix and skin has been well documented and its mechanism of action and interaction with tissue has been well described in the cervix.[3–5] VELscope is one such device that is designed to detect the innocuous lesions based on the principle of tissue fluorescence.

VELscope, the Visually Enhanced Lesion scope is a simple manual hand-held device that provides an easy-to-use adjunctive mucosal examination system for the early detection of abnormal tissue, including cancerous and precancerous tissue.[4,5] This device is developed by LED medical diagnostics in collaboration with the British Columbia Cancer Agency (BCCA).[4,5]It is an FDA approved device and it received 510(k) market clearance in April 2006.[6] It is based on the direct visualization of tissue fluorescence and the changes in fluorescence that results when abnormal tissue is present. These changes are detected by the operator viewing the tissues through a special scope.[4–6]

The VELscope is a portable device and it consists of a light source, light guide, a viewing hand-piece, a

disposable protective end cap for use with each patient examination, a tissue retractor, patient safety goggles and camera attachment for photo-documenting and monitoring the examination findings. It is designed for optimal flexibility and placement within the operatory.[7]

2 PRINCIPLE

Autofluorescence is the optical result of a complex interaction between wavelengths of light and tissue. The technology is based on the principle that normal cells will glow when exposed to fluorescent light, whereas abnormal cells will absorb fluorescent light and appear dark. The light-reflecting property of normal cells and the light-absorbing property of abnormal cells allow visual distinction of the two.[1–4] Each of the cells in human body contain molecules capable of self-fluorescence, especially when excited by specific light waves. These fluorescing products are numerous: tryptophan, porphyrins, collagen cross-links, elastin, nicotinamide adenine dinucleotide (NADH), and flavin adenine dinucleotide (FAD). Excitation and emission of fluorescence depends on how light is scattered and absorbed in tissue by these molecules. While scattering is caused by differences in the index of refraction of different tissue components, absorption is dependent on the molecular composition of the same component.[1,6,8,9] Mucosal abnormalities presenting with abnormal fluorescence patterns may arise from a variety of causes such as, increase in metabolic activity in the epithelium, breakdown of the fluorescent collagen cross-links in the connective tissue layer beneath the basement membrane, increase in tissue blood content or from the presence of pigments.[4,5,8,9]

The VELscope handpiece emits a cone of safe blue light (400-460 nm) into the oral cavity.[8,9] The light excites various molecules within the tissue from the surface of the epithelium through to the basement membrane and into the stroma beneath, causing them to absorb the light energy. As the tissue returns to normal energy levels, it re-emits the absorbed energy in the form of fluorescence. By utilizing special, selective narrow band optical filters in the handpiece, the different fluorescence response is viewed. Proper filtration is critical, as the intensity of the reflected blue-white light makes it otherwise impossible to visualize the narrow autofluorescent signal.[1] The healthy tissue shows up as a pale green glow and the suspicious region is identified by a loss of fluorescence, which appears dark.[1,3,4]

The deep penetration by VELscope can be a disadvantage in certain cases and hence some of the non-dysplastic tissues can show positive results as well. For example, hemoglobin, prominent vascularity as seen in cases with mild trauma or inflammation, melanin, aggregates of benign lymphoid tissue, due to the lack of collagen and leukocytes, due to the lack of autofluorescence, molecules may appear dark.[8,10] Bacteria using different fluorescent cytosol molecules will give red, pink or orange or yellow fluorescence, fungal microorganisms, such as candida, may fluoresce yellow or yellow/orange, irritation fibroma with secondary surface irritation and increased subepithelial vascularity and less irritated fibromas due to its high content of mature collagen may appear dark.[8,10] Based on the anecdotal experience of expertise using autofluorescing devices, a 0-4 point scale, with 4 representing complete loss of fluorescence, the autofluorescence outcomes with various oral lesions has been suggested to be 3-4 for dysplasia, melanosis, amalgam tattoo, tonsils, hemangioma, focal epithelial hyperplasia; 2-4 for geographic tongue, erosive lichen planus; 2-3 for irritational fibroma; 1-3 for squamous papilloma, inflammatory congestion and 0-1 for leukoplakia without dysplasia.[8] This indicates that even

nondysplastic tissue changes can be positive. However, they may not be true "false positives" and instead reflection of normal physiological or metabolical activities and hence interpreting their results require a basic understanding of common oral lesions, their pathophysiology and a closer evaluation with visible light.[8]

VELscope is used as an adjunctive aid along with traditional oral cancer examination with incandescence light, to aid in the early discovery and visualization of mucosal abnormalities that may not be visible to the naked eye. It is also used to assist surgeons to delineate lesional margins at the time of resection and for biopsy guidance.[4,11]

Comparatively VELscope has several advantages over other adjunct techniques. It is painless, non-invasive, chair side procedure that doesn't require any pre-rinses or stains. The examination takes less than three minutes and is easy to incorporate into the workflow. Camera adapter allows for photo documentation and tracking of lesions and disposable VELsheath/Barrier ensures asepsis.[5,7] Disadvantages of this device are, it requires relatively dark environment while examining and recording the lesions, the system is expensive and color interpretation is difficult.[10]

3 METHOD OF EXAMINATION

- A thorough visual examination is conducted and the findings are recorded.
- Intra-oral examination is performed using VELscope by viewing the oral cavity through the VELscope handpiece. A distance of approximately 2 inches (5 cm) from the oral cavity is maintained to optimize the visualization of the natural tissue fluorescence.
- Abnormal tissue typically appears as an irregular, dark area that stands out against the otherwise normal, green fluorescence pattern of surrounding healthy tissue.
- If a suspicious area is discovered, it is reevaluated under white light and VELscope and is photo-documented.[7]

Fluorescence Visualization (FV) needs to be differentiated with normal and few common conditions. The attached gingiva and anterior tonsillar pillars, often have a naturally darker appearance. Pigmented tissue usually appears dark under white light as well as under VELscope. Inflammation typically appears darker under VELscope due to the excess blood content. Hyperkeratosis may often appear bright under VELscope because of strong keratin fluorescence.[7]

It is suggested that an inflammatory lesion can be differentiated from dysplastic lesion by testing for blanching. The suspicious, typically darker area is observed through the VELscope handpiece while applying a light amount of pressure with the back side of an explorer or similar instrument in a sweeping motion to diffuse any blood from the area. If the normal green fluorescence returns with this pressure, then the lesion is of inflammatory in origin.[7,9]

4 DISCUSSION

Both fluorescence imaging and spectroscopy are being considered for cancer screening including that of oral cavity. While the fluorescence spectroscopy involves the exposure of tissues to various excitation wavelengths, fluorescence imaging involves the exposure of tissue to a rather specific wavelength of light.[1,2] Numerous studies have been carried out to evaluate the oral precancer-cancer diagnosing efficacy of VELscope. With earlier studies done mostly as case reports, the preliminary results were encouraging. However, the recent studies on general population with innocuous lesions have shown mixed results.[3,6,9,12–40] (Table 1).

One of the earliest studies conducted on 122 oral mucosal biopsies from 20 surgical specimens assessed for location, fluorescence status, histology and loss of heterozygosity. 32 of 36 Fluorescence visualization loss (FVL) biopsies showed positive histological changes. Molecular analysis on margins showed loss of heterozygosity (LOH) at 3p and/or 9p present in 12 of 19 FVL biopsies compared with 3 of 13 Fluorescence visualization retained biopsies. These data suggested that direct Fluorescence visualization can identify subclinical high-risk fields with cancerous and precancerous changes.[41] Furthermore there were numerous case series reported that demonstrated the usefulness of the instrument. Three cases with occult lesions were identified with fluorescence visualization during longitudinal follow-up, resulting in the diagnosis of a primary dysplasia, a second primary cancer and cancer recurrence in these cases. The ability to diagnose these oral diseases indicated the potential value of this technology in facilitating the detection of high-risk changes not apparent with regular clinical examination.[42]

Currently the research indicates that, there is no comprehensive agreement on the usage of VELscope in the detection of oral precancer and cancer. There is considerable variation in the sample and type of lesions considered in each study. It ranges from normal mucosa to oral lesions, keratotic or hyperplastic lesions, OPMDs, oral lichen planus, OSCC, with or without history of previous mucosal lesions or with previous history of OSCC.[3,6,9,12–40]

The recorded sensitivity and specificity varies widely. Lower specificity recorded in some of the studies indicate the high false positive rates associated with the device that dictates its cautious use and interpretation, especially keeping in mind the LAF associated with few normal and common benign conditions. While few of the studies have concluded VELscope to be used as an adjunct to the conventional white light screening wherein it enhances the sensitivity of the examination, others have contradicted it. It assists in defining the biopsy margins. Though the device may or may not be able to differentiate between benign, low risk and high risk lesions, it is definitely able to identify all high risk malignant lesions. It has been established as a simple noninvasive technique. However, biopsy and histopathology remains the gold standard.[6,9,12–40]

Presently, though the evidence supports its use in high-risk known malignant cases, its routine use in general practice remains uncertain due to the risk of false positives and high cost.Further studies with larger samples, standard criteria's and methodologies are required that takes account of different factors and variables that may influence the clinical appearance of the lesions, the associated metabolic and molecular variations and the optical properties of mucosa.Some authors are of the opinion that, the use of the VELscope device is highly subjective and strongly depends on the experience of the individual examiner with the device.Consequently, the use of this device requires training and experience.[6,9,12–40] Unlike the limited ability of VELscope, high-resolution imaging may provide a tool to discriminate benign changes, such as inflammation, from neoplasia with better specificity. Subsequently, the Multimodal optical imaging- a combination of wide-field autofluorescence and high-resolution imaging may yield the best sensitivity and specificity for detection of oral cancer.[16,24]

5 CONCLUSION

The prognosis of the deadly disease, the oral cancer can be improved only upon early diagnosis which is possible merely with the use of a suitable adjunctive technique that aids in its early diagnosis. Though numerous adjuncts are available, no definitive scientific evidence supports its regular use. VELscope, being the newer technique with v few scientific studies and the lack of scientific evidence, needs further substantiation. The use of this device also requires training and experience. Presently, the VELscope cannot replace the conventional clinical examination and consequently, complete clinical examination, followed by histopathological confirmation with the biopsy remains the gold standard for the diagnosis of oral precancer and cancer.

Table 1: Description of studies on use of VEL scope in oral lesions including precancer & cancer

Author & Reference No.	Year	Sample size	Nature of sample	Sensitivity	Specificity
Lane et al. [43]	2006	44	Severe Dysplasia/Carcinoma In Situ or invasive carcinoma, normal mucosa	98%	100%
Jayaprakash et al. [17]	2009	60	High risk patients with suspicious oral lesions, OPMD, OSCC	72%	50%
Roblyer et al. [18]	2009	65	Oral lesions & normal mucosa	95.9%	96.2%
Mehrotra et al. [6]	2010	156	OSCC, Epithelial dysplsia, benign Lesions	50%	38.9%
Koch et al. [19]	2011	78	Suspicious oral mucosal lesions including dysplasias & SCC	93%	15%
Paderni et al. [20]	2011	175	OPMD, OSCC	60%-75%	92.3%-97.4%
Awan et al. [12]	2011	126	White and red patches suspicious of OPMD	84.1%	15.3%
Matsumoto [21]	2011	74	OSCC, epithelial dysplastic lesions, Lichen planus	-	-
Scheer et al. [22]	2011	64	OPMD, OSCC	100%	80.8%
Babiuch et al. [23]	2012	50	OSCC	100%	12.5%
Farah et al. [15]	2012	112	OPMD	30%	63%
McNamara et al. [14]	2012	130	OPMD	66.7%	6.0%
Rana et al. [13]	2012	289	OPMD	100%	74%
Marzouki et al. [24]	2012	85	History of smoking, alcohol use, head & neck cancer	92 %	77%
Hanken et al. [3]	2013	120	OPMD	97.9%	41.7%
Petruzzi et al. [25]	2014	56	High risk oral lesions & lesions suspicious of SCC	70%-76.4%	51.3%-57.7%
Bhatia et al. [9]	2014	146	Oral mucosal lesions	64%	54.3%
Elvers et al. [26]	2015	20	Homogenous leukoplakia	-	-
Jena-Salas et al. [27]	2015	60	White, red and other oral lesions	40%	80%
Sawan et al. [28]	2015	748	Oral lesions	96.3%	74.1%
Kordbacheh et al. [29]	2016	42	Oral epithelial hyperplasia & dysplasia, oral lichen planus, OSCC	-	-
Ohnishi et al. [30]	2016	17	Severe Dysplasia/ CIS or Invasive Carcinoma	95%	100%
Scheer et al. [31]	2016	41	Multimodal treated cases of Oral Cancer	33.5%	88.6%
Burian et al. [32]	2017	90	Oral soft tissue lesions & CIS	-	-
Ganga et al. [33]	2017	200	Oral mucosal lesions	76%	66.29%
Huang et al. [34]	2017	140	Oral precancerous lesions & Oral cancer	97%	92%
Adil et al. [35]	2017	90	Tobacco associated oral white & red lesions, ulcerative lesions, malignant lesions	85.4%	75%
Yamamoto et al. [36]	2017	62	Leukoplakia, OSCC	-	-
Amirchagmaghi et al. [37]	2018	45	Malignant, premalignant & benign lesions	90%	15%
Canjau et al. [38]	2018	18	Premalignant & malignant lesions	94.4%	100%
Farah et al. [39]	2018	11	Oral epithelial dysplasia, oral lichen planus & lichenoid dysplasia	-	-
Belal et al. [40]	2018	30	Oral keratotic lesions	62.5%	71.4%

OSCC- Oral squamous cell carcinoma; OPMD- Oral potentially malignant disorder; CIS- Carcinoma in situ

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