

REVIEW ARTICLE

An update on intraoral application of colposcopy

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ABSTRACT

Colposcopy is an established technique for diagnosis in gynecology. Many premalignant and malignant lesions in these areas have discernible characteristics which can be detected using a colposcope, providing an enlarged view of the areas, allowing the colposcopist to visually distinguish normal from abnormal appearing tissue and take directed biopsies for further pathological examination. The diagnosis of a dysplastic lesion of the oral mucosa cannot be based solely on clinical findings. Therefore, histological evaluation of a representative biopsy specimen is necessary. The site for the biopsy is a subjective choice that sometimes raises doubts about its representativeness. So far, no simple and reliable method is available for selecting the most appropriate area for biopsy. Intraoral microscopy (oral application of the colposcopy technique) of mucosal lesions seems to offer advantages in selecting more representative sites for biopsy than routine clinical examination alone. The biopsy sites identified by direct oral microscopy show more advanced histologic signs than those selected by routine clinical examination. This article enlightens the application of colposcopy in diagnosis of oral premalignant lesions and malignant lesions.

Key words: Biopsy site, colposcope, colposcopy, oral cancer

INTRODUCTION

The incidence of premalignant lesions and oral cancers is steadily increasing globally. In spite of advancement in early detection, there is increased mortality and morbidity related to oral cancers.^[1] At present, though there are simple chair side methods including staining with toluidine blue and exfoliative cytology to localize a biopsy site, there is a high risk of false positives, which can be as high as 30%.^[2] And moreover, the diagnosis of a dysplastic premalignant lesion at the oral mucosa cannot be based solely on clinical findings. Therefore, a supplementary biopsy with a histopathological examination of the lesion is necessary to establish a definitive diagnosis. But, as biopsy site is a subjective choice, it is possible that biopsy specimens are taken from unrepresentative sites of the lesion or from sites where the morphologic changes cannot be detected. Hence, “biopsy site is the most reliable criterion for the correct diagnosis”. Colposcopy is a medical

diagnostic procedure to examine an illuminated, magnified view of the cervix, the tissues of the vagina and vulva. The word “colposcope” is derived from the Greek words kolpo means fold or hollow and skope means to examine.^[3]

Various authors have tried to adapt gynecologic methods of examination to the oral cavity as there is similarity between the two types of mucosa.^[4] Colposcope is a lighted binocular microscope connected to a video monitor which magnifies the area of interest 6–40 times its normal size.^[5] There are only a few studies which have described the value of direct oral microscopy in the diagnosis of oral mucosal lesions. Many premalignant lesions and malignant lesions in these areas have discernible characteristics which can be detected through the colposcopic examination. So it is one such method which is used to examine the mucosa for dysplastic changes and to select most appropriate site for biopsy.

So far, there is no reliable method applicable to the oral cavity that can replace a biopsy for a more definitive diagnosis of oral cancer, but some may be used as a supplement. Exfoliative cytology carries the risk of false-positive or false-negative results; a biopsy is necessary for final diagnosis. Toluidine blue may be used to identify a suitable site for biopsy, but studies have shown that the risk of false-positive staining may be as high as 30%.^[6] This is mainly caused by enhanced staining of ulcerations and by the filiform papillae of the

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tongue. Questions have also been raised regarding the risks associated with the use of toluidine blue because it shows an affinity for deoxyribonucleic acid (DNA).^[7]

Colposcopy is helpful in early diagnosis depending upon vascular pattern and it offers advantages in selecting most representative sites for biopsy than routine clinical examination alone and simple chair-side diagnostic methods.^[8]

HISTORICAL SURVEY

In 1924, Hinselmann was asked to write a chapter based on etiology, symptoms and diagnosis of uterine cancer in the third edition of the Handbook of Gynecology. Hinselmann faced this challenge most admirably. He was stuck by the limitations of palpation and naked eye examination in the early diagnosis of cervical cancer, which he believed could be improved only by optical aids. He felt it imperative to “provide on intense light source for the magnified image without sacrificing binocular vision”.

By 1925 he reported the construction of the first colposcope. For this purpose he attached a light source to the Leitz binocular dissecting microscope. He attached the optical system to a stand which allowed movement in every direction and also supplied a small screw for fine adjustment. After the invention of the colposcope, Hinselmann was able to state that “with regard to the so called early concerns, colposcopy enables detection of considerably earlier cases”. Even a tiny dot sized tumor did not escape detection. The magnification initially was 7.5 times. Thus, Hinselmann opened up a completely new field and based his ideas on appearances never seen before.^[5]

COLPOSCOPE AND COLPOSCOPY

Colposcopy is gold standard for examining the cervix, vagina and vulva under magnetization using an external white light source. Colposcope is a binocular microscope connected to a video monitor which magnifies the area of interest 6–40 times its normal size, using an external white light for illumination [Figure 1].

Types of colposcopes

The colposcopes are of two types:

- Those with a single objective lens with a fixed focal distance, whose magnification can be altered by changing the power of eyepieces
- Those with a single objective lens with a fixed focal distance, but with multiple magnifications possible by changing the setting of the knob or pressing a button.

Magnification

Multiple magnifications starting from $\times 5$ or $\times 7.5$ to $\times 20$ or $\times 30$ are preferred. The lowest magnification gives a bird's

eye view and is excellent for localizing or zooming in the area of interest. The magnification usually used for a detailed examination is $\times 15$.

The modern colposcope is based on the initial prototype, but differs from the original in that the magnification varies between 6 and 40 times as opposed to the initial 7.5 times. A 10 times enlargement is most suitable for routine use. Higher magnification enables recognition of minor features, but is not necessary for accurate diagnosis.

The most important accessories are the photographic equipment and the teaching arm. Simple low-power instruments without any accessories are also available, as well as more sophisticated ones with an electrically operated zoom lens and fine adjustment and camera. For routine use the simple colposcope is quite adequate, but for teaching both a camera and an observation tube are mandatory.

All colposcope have the objective lenses, the eyepieces, the filters, a light source and stand.

Objective lens

It influences the focal distance and therefore the working distance. The best focal distance is between 250 and 300 mm. This allows easy working and manipulation of the instruments without hampering the vision.

Eyepieces

Eyepieces should have the following good features;

- The axes of the eyepieces may be straight or inclined at 45° to the optical axis of the apparatus
- Features to adjust for the individual's interocular distance
- Must be fitted with rubber cups
- They should have independent focusing elements adaptable to the individual's eyesight
- Compensation for ametropia from $+ 7$ to $- 7$ diopters



Figure 1: CS-205 Colpo-Master™ II; A center post mount colposcope (Available from: <http://www.google.co.in>.)

- One very important feature is a convergent viewing beam for fatigueless operation.

Filters

Most colposcopes are fitted with green filters. These absorb the red light from color and enhance the image of the blood vessels which appear black. The contrast between normal and abnormal epithelia is also enhanced.

Light source

Light source should be a minimum of 30,000 Lux, should be centered permanently and should have a rheostat to alter the intensity of the illumination. Some colposcopes have the illumination automatically adjusted according to the magnification being used. Most of the colposcopes are fitted with a halogen bulb with strength varying from 6 to 12 V and 20 to 75 W.

Fiberoptic lighting is good. It is more expensive, but is cooler for the patient and the colposcopist.

A recent innovation is the light-emitting diode (LED), which is the preferred light source.^[9] These generate light by semiconductor processes and not by heating a wire filament, like in a halogen lamp.

Advantages of a LED light source are

- The luminous efficiency of LED is five to seven times higher than a lamp
- The LED light offers, by using a different optical system, substantially improved contrast and with it a sculptural impression is obtained even on two-dimensional (2D) photos
- The life span of LED is many times higher (up to 10,000 h) than a halogen lamp. It works out to roughly 10 years at a daily usage of 4 h.

Photo and video colposcopes

These are more expensive than the standard colposcopes. Some features include:

- Capability of taking stereoscopic pictures, that is, double-picture format. One photograph can be given to the patient and one can be kept for teaching and as a record in the office file
- Still and video photography is possible at different magnifications.

Applications of colposcopy include

The main purpose of colposcopy is to detect intraepithelial neoplasia and early neoplasia of the cervix, vagina and vulva.^[10] Colposcopy is used for following:

- As an integral part of every gynecologic examination in concert with cytology

- To display and localize lesions suspected cytologically
- To clarify the nature of clinically suspicious lesions
- As a part of a sexual assault investigation in forensic examination
- It is also used to diagnose lesions due to human papillomavirus infection.^[11]
- Changes associated with immunosuppression such as human immunodeficiency virus (HIV) infection, or an organ transplant patient.^[12,13]

PROCEDURE

Then mucosa is rubbed with large cotton swab soaked in 3% acetic acid for a minute and then visualized through colposcope. The magnified images are viewed on monitor and saved for record purpose.^[14]

Effect of epithelium on the colposcope image

The colposcopic image is the result of the reciprocal relationship between the epithelium and the stroma. The epithelium acts like filter through which both the incident and the reflected light pass.^[15] The epithelium is colorless and the stroma is red because it contains blood vessels. The redness of the stroma is transmitted through the epithelium and is visible through the colposcope. The intensity of color represents the ratio of reflected and absorbed light and is related to:^[15-17]

- The number of layers of epithelium
- The optical density of the epithelium (i.e. the morphology and the organization of the epithelial cells)
- The vascularity and the nature of the underlying stroma
- Tissue chromophores
- The amount of hemoglobin.

The application of 3–5% acetic acid alters the epithelial surface. The effect is due to reversible coagulation of the nuclear-proteins and cytokeratins.^[18,19] Burke *et al.*, believed that the reaction is due to a reversible osmolar change resulting in cytoplasmic dehydration and cytoplasmic membrane collapse.^[17] This cellular change produces more reflected light and the colposcopic image is white. This acetowhite effect is transient and the speed with which it appears and disappears depends upon the nuclear-cytoplasmic ratio and the number of cells. The immature metaplastic epithelium turns shiny white color that disappears fast, whereas an opaque and long-lasting acetowhiteness is seen in areas of high-grade intraepithelial neoplasia.

VASCULAR PATTERN SEEN UNDER COLPOSCOPE

The vascular changes described in colposcopic study can be used as the criteria for selecting biopsy sites in the oral cavity. They include the vascular pattern, intercapillary distance, surface pattern, color tone and opacity, as well as the clarity of demarcation of the mucosal lesions. In the normal mucosa of

uterine cervix, two basic types of capillary network can be seen: Network capillaries and hair pin capillaries.^[8] [Figure 2].^[17] The whiter and more opaque features of lesions associated with dysplasia or carcinoma *in situ* can also be distinguished. The abnormal colposcopic findings are:^[20]

Acetowhite epithelium

Flat acetowhite epithelium

Areas of high nuclear activity appear white after application of 3–5% acetic acid. A mild degree of acetowhiteness occurs in areas of immature metaplasia, which appears slowly and disappears fast.

Dense acetowhite epithelium

High-grade cervical intraepithelial neoplasia (CIN) or cancer is generally associated with a dense acetowhite change that appears fast and persists longer. Dense acetowhite change within columnar epithelium may indicate glandular disease [Figure 2] [Table 1 and 2].^[17]

Punctuation

If the tips of the terminal vessels in the stroma reach the surface of the epithelium through stromal papillae, they will appear as red dots prior to the application of acetic acid. This colposcopic image is called punctuation [Figure 2] [Table 1 and 2].

Fine Punctuation: The finer the punctuation, it is more likely that the lesion is high-grade CIN.

Coarse punctuation: The coarser the punctuation, it is more likely that the lesion is high-grade CIN or cancer.

Mosaic

If the vessels do not reach the epithelial surface but extend only partially into the epithelium, they appear as red lines surrounding blocks of epithelium. The colposcopic image resembles tiles of a floor and it is termed as mosaic pattern. The appearance is accentuated after application of acetic acid [Figure 2].^[17]

Fine mosaic; the smaller, smoother/finer the mosaic, the more likely the lesion is of low-grade CIN or metaplasia.

Coarse mosaic; the coarse, wider and more irregular the mosaic, the more likely the lesion is of high-grade CIN or invasive cancer [Figure 2] [Table 1 and 2].^[17]

Atypical vessels

These vessels appear to be running on or parallel to the surface of the epithelium and are of irregular caliber and branching. They appear like coarse wide hairpins and commas, corkscrews, waste paper, coarse and caliber tree-like and root-like forms or spaghetti-like forms. These vessels are usually indicative of invasive cancer [Figure 2] [Table 1 and 2].^[17,21,22]

Colposcopic features suggestive of invasive cancer:^[20]

- Irregular surface contour, erosion or ulcer
- Dense acetowhite change
- Wide irregular and coarse punctuation and mosaic pattern
- Atypical vessels.

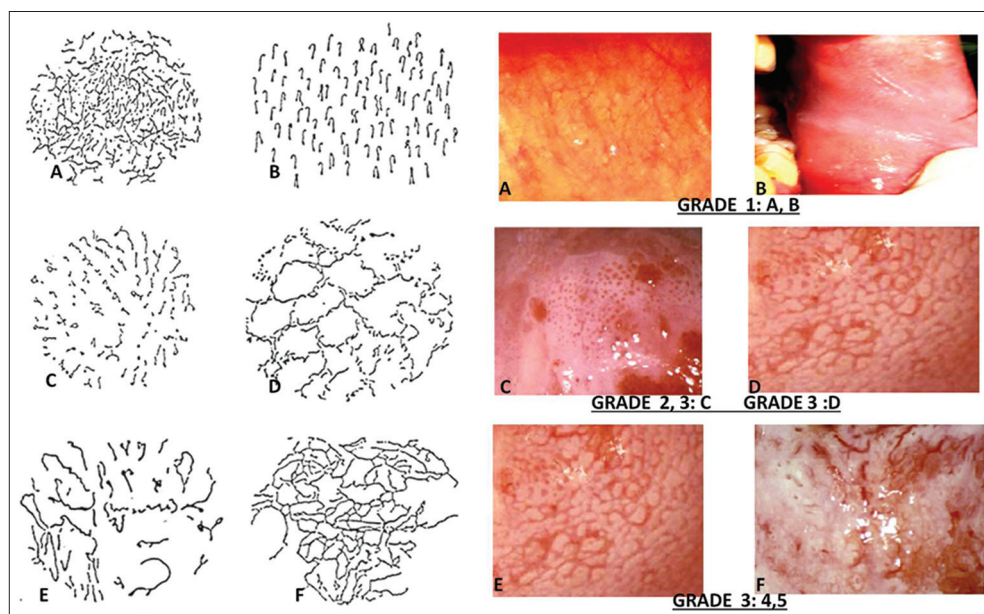


Figure 2: Precancerous Colposcopic patterns. (a) Network capillaries, (b) hairpin capillaries, (c) punctuation capillaries, (d) mosaic capillaries and (e and f) atypical capillaries

ASSESSMENT AND INTERPRETATION OF ABNORMAL COLPOSCOPIC FINDINGS

Colposcopic appearances used in the interpretation of abnormal colposcopic findings include:^[20,22-25]

- Response to acetic acid
- Surface contour
- Margin of lesion
- Punctation, mosaic and intercapillary distance
- Appearance of blood vessels (including atypical blood vessels)
- Appearance of gland openings
- Iodine uptake
- Keratosis.

Grading and scoring systems:

For colposcopic examination in gynecology[Figure 2]^[22,26]

I Grading system of coppleson et al.

Grade1 (insignificant, not suspicious)

Ace to white epithelium, usually shiny or semitransparent, borders not necessarily sharp, with or without fine caliber vessels, often with ill-defined patterns, absence of atypical vessels; small intercapillary distance.

The predicted histology is metaplastic epithelium (both immature and mature), acantholytic epithelium,

subcincinal papillomavirus infection (SPI) and low grade CIN (CIN1).

Grade2 (significant, suspicious)

Acetowhite epithelium with greater opacity with sharp borders; with or without dilated caliber, regularly shaped vessels; absence of atypical vessels; usually increased intercapillary distance. The predicted histology is high-grade CIN (CIN2or 3).

Grade 3 (Highly significant, highly suspicious)

Very white or gray opaque epithelium; sharply bordered; dilated caliber, irregularly-shaped, often coiled, occasionally atypical vessels; increased but variable intercapillary distance and sometimes irregular surface contour (microexophytic epithelium).

The predicted histology is CIN3 or early invasive cancer. The latter diagnosis is probable in the presence of atypical vessels and microexophytica.

II Combined colposcopic index by Reid and Scalzi

The grading system is presented in Table 1.^[23]

III Grading system of Burke and co-workers:

The grading system is presented in Table 2.^[17]

The field of ophthalmology utilizes high magnification

Table 2: Reid and Scalzi proposed a scoring system to predict the histologic diagnosis on the basis of four colposcopic features

Colposcopic sign	Zero point	One point	Two points
Margin	Condylomatous or micropapillary contour indistinct acetowhitening flocculated or feathered margins. Angular, jagged lesions, satellite lesions and acetowhitening that extend beyond the transformation zone	Regular lesions with smooth, straight outlines	Rolled, peeling edges internal demarcations between areas of deferring appearance
Color (after application of aceto white)	Shiny, snow-white color indistinct acetowhitening	Intermediate shade (shiny gray)	Dull, oyster-white
Vessels	Fine-caliber vessels, poorly formed patterns; condylomatous or micropapillary lesions	Absentvessels	Definite punctation mosaic
Iodine	Positive iodine staining	Partialiodine uptake	Negative staining of significant lesion

Scores of 0-2 are predictive of a minor lesion (HPV or CIN), scores 3-5 usually indicates a middle-grade lesion (CIN2) and scores of 6-8 usually indicate significant CIN (CIN2 or 3). HPV: Human papillomavirus; CIN: Cervical intraepithelial neoplasia

Table 1: Burke and coworkers have recommended a grading system to predict the underlying lesion

Grade	Surface	Margin	Color	Time	Vessels	Pathology
1	Flat	Indistinct	Normal/ slightly white	Appears slowly, remains for short time, disappears rapidly	Fine with normal ICD	SPI, inflammimmat metapl, pregnancy, regeneration, repair
2	Flat	Distinct	Whiter	Average time to appear, remains for several minutes, disappears with average speed	Punctations, mosaics lightly increased ICD	SPI, CIN1 and CIN2
3	Raised	Sharp	Whitest	Appears rapidly, stays a long time, disappears slowly	Coarse punctuations and mosaic, increased ICD, atypical vessels	CIN3

CIN: Cervical intraepithelial neoplasia; SPI: Subcincinal papilloma virus infection; Inflamm: Inflammation; Immat metapl: Immature metaplasia; ICD: Intercapillary distance

microscopes to see minute capillary changes to aid in accurate diagnosis and treatment planning. In gynecology, microcolpohysteroscopy and colposcopes have been used for decades. With the help of Papanicolaou smears from the visualized sites an early diagnosis and adequate follow-up of cervical cancers have been possible. This has decreased the incidence of cervical cancers from 40 to 3 to 7%.

Applications of colposcopy in oral cavity

In oral cavity, colposcopy allows noninvasive examination of the oral tissues *in situ* at high magnification and has good resolution. Surface topography and the degree of keratinization of the epithelium may be readily observed and documented.

Three-dimensional observations of such structures as the papillae of the tongue are possible because of the depth of field combined with good resolution.

Because the instrument allows simultaneous viewing of surface cells of submucosal vessels, it is hoped that techniques will be developed for documentation without the need for vital staining.

An important area of application may well be in the diagnostic evaluation and monitoring of treatment of oral cancer. Areas of surface dysplasia could be mapped to indicate the full extent of epithelial change before biopsy and surgery.^[27-30]

The comparative effects of different treatment modalities, such as radiation and chemotherapy, on the junction between the tumor and normal tissue could also be studied.^[27] Most patients with malignant and premalignant conditions show changes in the vascular picture which can be easily appreciated well by direct oral microscopy. In a recent study, Pazouki *et al.*, concluded that there was a close relation between vascularity and tumor progression in the oral mucosa.^[28] Many patients with oral squamous carcinomas have a marked inflammatory infiltrate; this inflammation interferes with the evaluation of dysplastic changes. In comparison, a biopsy specimens selected by colposcopy rarely shows a severe inflammatory infiltrate.^[29]

DISCUSSION

Tumors arising from the oral cavity are usually well advanced at the time of diagnosis. Prognosis of squamous cell carcinoma (oral cavity and pharynx) depends on early diagnosis, despite advanced surgical techniques and adjuvant treatment, the 5-year survival rate remains ~40–50%.^[3] The disease is life-threatening, with high morbidity resulting from late treatment. However, if it is diagnosed at an early stage, oral cancer is often curable and inexpensive to treat.^[1]

The clinical examination is one of the best modalities in suspecting the pathology, but the biggest disadvantage in the diagnosis lies in deciding the site of biopsy in early lesions and sometimes whether or not a biopsy is required in these lesions.

Early stages are difficult to detect as the lesion may not be palpable and color changes are not very different from the color of the surrounding mucosa. Thus, identifying clinically suspicious/undetectable lesions has gained importance, whereby diagnosis can be confirmed by biopsy at an earlier stage.^[1] In developing countries such as India, where there is high prevalence of disease, the focus is on downstaging oral cancer at diagnosis from advanced to earlier disease. It is assumed that if premalignant lesion is detected and treated, the lesion may not progress to cancer.^[5] In the past decades, adjunctive techniques have emerged with claims of enhancing the oral mucosal examinations and facilitating the detection of and distinctions between oral benign, oral premalignant and malignant lesions.^[5] Techniques that are promoted or assessed to improve earlier detection and diagnosis of oral malignancy include toluidine blue, vizilite plus with toluidine blue, velscope brush biopsy, etc.

Toluidine blue is a cationic metachromatic dye that may selectively bind to free anionic groups such as sulfate, phosphate and carboxylate radicals of large molecules.^[6,31] It has been used for decades as an aid to the identification of mucosal abnormalities of the cervix as well as in the oral cavity. It has been valued by surgeons as a useful way of demarcating the extent of a lesion prior to excision.^[7] Toluidine blue staining is considered to be sensitive in identifying early oral premalignant and malignant lesions.^[3] Unlike direct oral microscopy, toluidine blue does not need expensive equipment and is therefore much simpler and less costly, but the risk of false-positive staining can be as high as 30%. Ten questions have also been raised about the risks associated with the use of toluidine blue because it shows an affinity for DNA.^[22]

Evidence-based recommendations for mass screening of oral precancer and cancer have been laid out, which highlights the use of newer techniques. Devices like ViziLite® Plus and Orascoptic utilize the property of tissue reflectance, whereas devices like VELscope® based on autofluorescence, are marketed as an adjunct to visual examinations in the identification of oral mucosal abnormalities. Capillary changes precede tumor growth, with the pattern of tumor angiogenesis being different from the usual neovascularization taking place during repair and regeneration procedures. At a cellular level, various molecules such as vascular endothelial growth factor, basic fibroblast growth factor and transforming growth factor alpha are implicated; but the clinical perceptibility of these altered vascular patterns is poor. Direct optical visualization of these patterns would be helpful in early determination of the underlying pathology and also aid in marking out the site for biopsy.^[31,32]

Hopefully, direct oral microscopy will be used to follow mucosal lesions and detect signs of progression because at present this seems to be the only way to evaluate vascular changes in the oral mucosa. Compared with staining with toluidine blue, this may be the main advantage of using direct oral microscopy. The

chief disadvantages are the complexity and cost and these should be evaluated by further comparative studies. This complex diagnostic methodology would, in the future studies, require analysis on a larger sample size with added filter modifications for typifying exact vascular pattern modifications. The finesse of judgment should not be compromised owing to the time factor, while screening large population. However, the cost of the equipment is not a big drawback compared to its advantage in terms of visualization and precision in clinical diagnosis.

The question remains of whether the advent of such microscope-aided precision dentistry equipment in dentistry heralds the end of direct visualization/naked eye working. The advantage would be better selection of the biopsy site compared with naked eye selection, which would help improve diagnosis and treatment planning of oral premalignant and malignant lesions. Ellen H Hopman and Helmerhorst TJM, concluded from their study that colposcopy was an effective tool for diagnosing cervical intraepithelial neoplasia. (Hopman and Helmerhorst 2005)³⁰. They also suggested that microinvasive carcinoma was suspected when mosaic, punctation and acetowhite epithelium were seen with a thick white epithelium that had a clear and elevated margin with an irregular surface contour and raised capillaries. Shetty *et al.*, also concluded from their study that the histopathological assessment of a biopsy specimen is regarded as the most reliable criterion for a correct diagnosis in cases of epithelial dysplasia; consequently the specimen must be taken from the most representative area of a suspicious looking lesion for increasing the diagnostic accuracy (Shetty *et al.*, 2011).^[26]

SCOPE OF COLPOSCOPE IN FUTURE

It is consider that this instrument may bridge a gap between microscopic examination of the surface morphology of the oral tissues and histological examination for teaching purposes, the instrument could be combined with video techniques with appropriate video recording equipment and quality photographic records may be obtained from individual frames. Oral microscopy will be used to follow mucosal lesions and detect signs of progression because at present this seems to be the only way to evaluate vascular changes in the oral mucosa. Compared with staining with toluidine blue, this may be the main advantage of using direct oral microscopy. The chief disadvantages are the complexity and cost and these should be evaluated by further comparative studies.

In conclusion, direct oral microscopy can be used to select biopsy sites. This method should be evaluated in further clinical studies and compared with the use of various staining methods.

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