Original Research Paper
Dental Science

Colposcopy in Screening Dysplastic Lesions of Oral Cavity: A Study.

DR. PALLAVI KESARWANI MDS SENIOR LECTURER, DEPT. OF ORAL PATHOLOGY & MICROBIOLOGY, HAZARIBAGH COLLEGE OF DENTAL SCIENCES, HAZARIBAGH, JHARKHAND.

DR. ANAND CHOUDHARY MDS READER DEPT. OF ORAL MEDICINE & RADIOLOGY, HAZARIBAGH COLLEGE OF DENTAL SCIENCES, HAZARIBAGH, JHARKHAND.

ABSTRACT

Background: Oral cancers are believed to develop from pre-existing oral premalignant lesions & conditions so an early detection of these can definitely improve survival rate. The diagnosis of malignant and potentially malignant epithelial lesions (PMEL's) of the oral mucosa (OM) cannot be based alone on the clinical findings (CF) only, histologic evaluation is the gold standard for it. Therefore, the selection of a representative biopsy site plays a significant role. However the site for the biopsy is always a subjective choice of the surgeons that may raise doubts about its representativeness. Colposcopy, a well-known gynecological diagnostic procedure, enables evaluation of changes in surface topography and vascular patterns of the lining mucosa thus helping in selecting the most appropriate site of biopsy.

Aim: The present study assesses the representativeness of colposcopic guided biopsy sites from the sites selected solely on routine clinical examination in malignant and PMEL's.

Methods: The study included 30 subjects aged between of 30-60 years comprising of 10 cases each of oral submucous fibrosis (OSF) and hyperkeratotic lesions (6 homogeneous and 4 speckeld leukoplakias), 6 cases of oral lichen planus (OLP) and 4 cases of clinically suspected oral squamous cell carcinoma (OSCC). 15 healthy, age-matched individuals were kept as a control group. Each patients were subjected to a thorough clinical examination followed by colposcopic examination of oral cavity. The biopsy was then performed on the representative site selected and later the histopathologic findings were compared in the two techniques.

Results: The sensitivity and specificity of biopsies performed on the basis of colposcopic examination came out to be 64% and 93% respectively with a positive predictive value of 90% and a negative predictive value of 75% were reported. Thus colposcopic guided biopsies were more appropriate than on the basis of CF alone.

Conclusion: The study enlightens on the most recent insights into cancer diagnostics. To facilitate a better systematic approach, with newer methodologies that ensure patients receive a prompt diagnosis and adequate treatment.

KEYWORDS : Colposcopy, potentially malignant lesions, biopsy, vascular pattern

INTRODUCTION

Early precancerous lesions & conditions are often subtle and asymptomatic. Therefore, it is important for the clinician to maintain a high index of suspicion, especially if risk factors such as tobacco use or alcohol abuse are present.[1] OSCC is one of the predominant causes of death worldwide accounting for more than 90% of all the cancers affecting the oral cavity.[2] Visual inspection alone in oral cancer screening often tends to miss areas in the lesion having dysplasia or early cancer, This is especially true for innocuous looking lesions which are subjected to "watchful waiting" and close follow-up despite the fact that some precancerous and cancerous cells within them remain undetected and are allowed to progress to a more advanced stage thus limiting treatment options.[3] Therefore early diagnosis of these lesions beholds paramount importance in significantly improving the survival rates in these patients.[4]

There is always a need for a non-invasive technique for detection of dysplastic changes that may assist the clinician in choosing an appropriate biopsy site, thus helping in early detection and treatment. Colposcopy is a gynecological diagnostic procedure to examine an illuminated, magnified view of the cervix and the tissues of the vagina and vulva.[5] Colposcope is a microscope which allows the epithelium to be viewed at 6-40 fold magnification. It is mounted on a free and movable stand its lens has a focal length ranging between 20-30cm. It has a binocular eye piece attached to it and a blue green filter is placed between light source and objective lens which absorbs red light so that blood vessels appear much darker.**(Fig 1)** Colposcopy enables evaluation of vascular and surface pattern, inter-capillary distance, color tone and opacity, as well as clear demarcation of the mucosal lesions thus helps in selecting the most appropriate site of biopsy that may reveal epithelial dysplasia.[6]

Various authors have explored it as a useful chair-side adjunct in the early diagnosis of premalignant and malignant lesions of the oral mucosa because of the similarities between the two mucosas.[7] Various studies have reported accuracy of colposcopic examination for the detection of mucosal changes lying between 70% and 98%.[8-9] In view of the need of a non invasive simple technique for early and accurate assessment of malignant and PMEL affecting the oral mucosa. The present study has been planned to assess the significance of colposcopic examination in the oral mucosa and to evaluate its usefulness in early diagnosis and treatment.

MATERIALS AND METHODS

Source of data

The current in-vivo study was performed for a period of one year in the Department of Oral Medicine and Radiology, College of Dental Sciences, Davangere and Department of Obstetrics and Gynecology, JJM Medical College, Davangere. The subjects were selected from those attending the Dental College OPD during the period of April 2006 to April 2007. The study protocol was approved by the Institutional Ethical Committee and a detailed informed written consent was obtained from all the subjects included in the study.

Inclusion and exclusion criteria

Inclusion criteria included clinically diagnosed cases of premalignant lesions (homogenous and non-homogenous leukoplakia), premalignant condition (OSF and OLP) and OSCC of buccal mucosa with minimum extension of 2 x 2cm or more. Patients with systemic diseases, lesions with secondary infections, and undergoing active treatment of oral mucosa were excluded from the study.

Methodology

The study comprised of 30 patients based on inclusion and exclusion criteria with age range of 30-60years, including 10 cases each of OSF and hyperkeratotic oral lesions including homogeneous and non-homogeneous leukoplakias, 6 cases of OLP and 4 cases of OSCC based on clinically examination. 15 healthy, individuals of similar age range were kept as a control group. The significance of samples size was analyzed statistically before their inclusion in the study. In all the subjects, a detailed case history and thorough clinical examination of the intra oral lesion was performed. Clinical examination was followed by colposcopic examination of the lesions, thus the most representative site for biopsy were selected.

Colposcopic examination

After clinical examination, the mucosa was wiped with saline as abnormal epithelium appeared much darker than the normal epithelium. At higher magnification, using blue green filters the abnormal vascular patterns were evaluated with the help of a Colposcope.(Fig 1) Now, 4% acetic acid was applied to the lesion for about a minute which causes transient coagulation of nuclear proteins, as the dysplastic cells contain larger amount of chromatin the lesion takes up the stain and ultimately becomes acetowhite. These areas with alterations were selected for biopsy.[10]

If no lesions were visible after acetic acid application then Lugol's solution was used for further examination of abnormalities. Staining of the Lugol's iodine is based on glycogen content of the epithelium. As the inflammatory or carcinomatous epithelium has got higher glycogen content than the normal epithelium this helps in delineating normal from abnormal epithelium. The brown stained areas were considered as positive lesions while the unstained areas were considered as negative.[10]

Two basic types of capillary patterns can be seen on the normal mucosa of the uterine cervix, with direct microscopy i.e. network capillaries and hairpin capillaries. A characterstic vascular pattern, punctation (previously called ground), is seen in areas of dysplasia and carcinoma *in situ.* Punctation pattern manifests as dilated and twisted irregular hairpin-type vessels. Another pattern of vessels seen in dysplasia is called mosaic this pattern develops if the vessels are unable to reach the epithelial surface but extends partially in the epithelium, they appear as red lines making blocks of epithelium, acetic acid application, further accentuates it forming a typical honeycomb pattern because of acetowhiteness of the atypical epithelium. When the pattern were different from either of two types it was considered as atypical vessels. In areas of dysplasia, carcinomain-situ or malignancy, punctation, mosaic or atypical patterns are encountered.[11-13] Therefore, the presence of any of the altered vascular pattern warrants for histopathology.

When the area selected by clinical criteria and colposcopic examination was superimposed, then only one common biopsy sample was obtained but in case if two different areas were selected from the same lesion, then they were marked with two different colors, and the biopsied tissue were send for histopathological evaluation. Comparison of histopathlogical diagnosis obtained with routine CF and colposcopy was performed, and the data was subjected to statistical analysis.

Result

The present study comprised of 30 subjects. Based on clinical examination 10 cases were of oral leukoplakia (6 homogenous and 4 speckled) (Fig 2A), 10 cases of OSF, 6 cases of OLP (Fig 2B) and 4 cases of OSCC (Fig 2C). On comparing the histopathological findings observed in the biopsy specimen based on clinical and colposcopic presentation were as follows:

The biopsy performed on the basis of clinical presentation showed a sensitivity of 25.5% and a specificity of 75% and a positive and negative predictive value of 50% and 55.5% respectively whereas the colposcopically directed biopsy showed a sensitivity and specificity of 64.29% and 93.75% while the positive and negative predictive value of 90% and 75% correspondingly **Table 1.**

The diverse vascular patterns seen in patients have been depicted in **Tables 2.**

Discussion

Despite numerous recent advanced techniques in early detection, still a dramatic increase in incidence of PMEL's and OSCC is seen globally. Leukoplakia associated with dysplasia is one of the commonest PMEL seen in the oral cavity.[14] The rate of occurence of dysplasia in oral leukoplakia varies between < 1 and > 30%. The malignant transformation rate of homogeneous leukoplakias is about 5% & four to five times higher risk of malignant development is generally seen in the non-homogeneous leukoplakias as compared with the homogeneous type.[15] OSMF is a precancerous condition affecting 5 million young Indians and has a prevalance of malignant transformation between 0.03% - 3.2% in India.[14] According to an Indian study at four urban centers, the prevalance of *malignant transformation in* OLP varies between 0.02%-0.4%.[15]

Though carcinoma of the oral mucosa can easily be recognized based on CF, when the lesions is noticeably invasive, associated with pain and coupled with functional restraint or regional lymphadenopathy. Conversely, it is hard to detect dysplasia and carcinomas harboring in potentially malignant epithelial lesions and early invasive carcinomas of the oral cavity. With an aim of improving the efficiency of these diagnoses, numerous techniques are being developed like toluidine blue vital staining, exfoliative cytology, autofluorescence, oral brush biopsy, acetic acid staining, chemiluminescence etc.which has been advocated to complement clinical examination and to facilitate the identification of early dysplastic changes and initial carcinomas. But in contrast, many studies have shown that these are not accurate to establish a final diagnosis and gives false positive or false negative results at a rate of 30%.[16-18] Henceforth final diagnosis is still dependent on histopathologic examination of biopsied specimen. Therefore selection of the biopsy site is still a critical choice as biopsy from a non-representative area may be misleading, there is a need for a non-invasive technique for detection of dysplastic changes that may assist the clinician in choosing an appropriate biopsy site thus ultimately saving the patients from the trauma of multiple biopsies and thus helping in broader range of diagnoses.[19]

Colposcopic assessment is a non-invasive, painless procedure without any prerequisite of anaesthesia. Since ages it has been an established technique to examine an illuminated magnified view of vagina or cervix with good resolution. The first colposcope was constructed by Professor Hans Hinselmann of Hamburg, Germany in 1925.[6] It was first used by Goran Gynther in the year 2000, for the examination of oral mucosal lesions.[20] In a previous study, in the detection of cervical cancer, Sankaranarayanan from India have reported the sensitivity and specificity of 4% acetic acid as 88% and 78% respectively. Resemblance of oral epithelium with cervical epithelium created the ground for its use in oral cavity.[21]

Application of 4% acetic acid to the oral mucosa for 30seconds, coagulates the mucus, which then can be easily removed followed by swelling of squamous epithelium thus reducing its transparency and causing reversible coagulation of nuclear proteins. The region turns white after application of 4% acetic acid for 30seconds and is termed as aceto-white lesions. It bears no affect on the mature, glycogen-producing epithelium as the acid does not infiltrate below the outer one-third of the epithelium. Cells of normal mucosa have small nucleus and large quantity of glycogen. Henceforth the dysplastic cells are affected the most since they contain large amounts of abnormal chromatin.[10] According to Burke et al. the reaction is a result of a transient osmolar change which leads to cytoplasmic dehydration and membrane collapse. The altered cellular architecture produces more reflected light, thus producing a white colposcopic image.[22] The epithelium being colorless acts as a filter through which both the incident and the reflected light passes. The image seen through colposcope is based on the reciprocal relationship between, the surface configuration of the tissue, its thickness, morphology, architecture of epithelium, vascularity of the underlying stroma, sum of tissue chromophores and also on the quantity of haemoglobin.[22-24] The rate of appearance and disappearance of the aceto-whiteness depends on the number of cells and nucleo-cytoplasmic ratio. In case of immature metaplastic epithelium whitening disappears faster, while an opaque and long-lasting aceto-whitening is noted in the areas bearing high-grade malignancy.[25] However, studies have shown that chronic trauma, chemical and mechanical irritation, such as that related to the use of tobacco, also cause increased aceto-whitening effect. If lesion is not discernible after acetic acid application then further examination can be done using Lugol's or Schiller's solution. Staining with Lugol's iodine is dependent on the amount of glycogen and as the content of glycogen is higher in normal epithelium it stains brown whereas the inflammatory or carcinomatous epithelium has reduced glycogen, so it does not retain the stain.[10] Hence forth, the use of acetic acid and Lugol's solution aids in the better visualization of abnormal areas in the mucosa. Just as the aceto-whiteness begins to fade, the vascular patterns become clearly visible, thus the areas depicting abnormal vascular pattern are often considered for biopsy.

On application of 4% acetic acid over hyperkeratotic lesions we observed a white raised lesions with raised, papillary borders which was a consistent finding visualized various other authors like, Albert Schmitt 1959,[26] Rene Cartier 1977[27] and John Marlow 1979[28]. The lesion appeared aceto-white with 4% acetic acid and was iodine negative and straw-colored on Lugol's iodine application. Out of the 10 cases of leukoplakia, 50% and 80% of the patients were correctly diagnosed histopathologicaly based on clinical and colposcopic examination respectively. However, there is limitation in cases of leukoplakia and other hyperkeratotic lesions as hyperkeratosis may cover up the exact histopathological findings of epithelial dysplasia in the subsequent sub-surface layers of the epithelia, thus mandating all leukoplakic lesions to be biopsied as directed by colposcopic examination or, performing multiple biopsies specimens, lastly repeat biopsy in cases of high suspicion.[27]

On applying of 2% acetic acid on OSF lesions it appeared as faint pink in color. The Lugol's iodine uptake was not uniform and at few places, it was iodine negative. On histopathological evaluation of 10 cases OSF, 40% and 70% of the cases were correctly diagnosed based on clinical and colposcopic examination respectively.

OLP colposcopicaly appeared as aceto-white raised striae with intermediate areas showing few thin vessels. On histopathological examination, the accuracy on clinical and colposcopic examination was reported as 50% and 83.3% respectively.

OSCC colposcopically revealed aceto-white and iodine negative picture, thus appeared to harbour high grades of epithelial dysplasia. On histopathological correlation an accuracy of 100% on colposcopic and 75% on clinical examination was reported. The capillary alteration subsequent to tumor enlargement outlines the pattern of tumor angiogenesis which is truly different from normal neo-vascularization that happens in repair and regeneration processes. Stereoscopic magnification produced by colposcope enables the surface contour to be visualized thus helps in early determination of the underlying pathology and also aids in demarcating the biopsy site.[29] In the present study on histopathological correlation we observed that the biopsy specimens selected according to colposcopic criteria reported an accuracy of 100% while it was only 75% based on clinical examination. For that reason, colposcopically guided biopsies are found to be more representative from the ones simply based on CF. The altered vascular patterns assisted in the correct choice of the biopsy site, which in turn avoided chances of reporting false-negative results. In majority cases of OSCC presence of marked inflammation interferes in the evaluation of dysplasia within the lesion.[20] In contrast, biopsy specimens selected through colposcopic examination overcome this most common problem as there is lack of glycogen in such tissue so application of Lugol's iodine will not stain them thus their relative whiteness is maintained; this aids in discriminating chronic inflammatory lesions from dysplastic lesions.[10] At times few polymorphous lesions may show distinct colposcopic lesions without significant alteration in tissue histology. These lesions may signify epithelium with a higher risk of malignancy and require a close monitoring and a careful follow-up for probable conversion of dysplasia, carcinoma-in-situ or invasive carcinoma in the near future.[30]

The sensitivity of a colposcopic examination defines the proportion of patients with the disease whose colposcopic appearances were also positive for the disease while the specificity of a diagnostic test evaluates the proportion of the subjects without the disease and whose colposcopic appearances are also negative for the disease. The present study reported a sensitivity of 64% and a specificity of 93% regarding the selection of biopsy site. Consistent results have been reported in previous literature too, by Gynther in 2000 and Shetty in 2011 regarding significance of colposcopy in cancerous and pre-cancerous lesions of the oral cavity. The predictive value defines the usefulness of such a test for screening purposes i.e. probability of being abnormal/ normal or if it is positive/negative. In the present study a positive predictive value (+ve) of 90% and a negative predictive value (-ve) of 75% is reported. [Table1] From the above findings it can be cited that 'colposcope' can act as an important adjunct and screening tool and has got a superior edge over clinical examination in selection of appropriate sites for biopsy.

Conclusion

Early detection preferably at an early pre-invasive stage goes a long way to cure the disease or to have a good prognosis. Colposcopy is definitely emerging as a new ray of hope in early detection of premalignant and malignant oral mucosal lesions, all because of its high precision, versatility, easy to use and non-invasive properties. Although this technique needs to be evaluated in further clinical studies with larger sample size and comparative evaluation with other existing advanced methods to check its efficacy and accuracy which in turn may improve the treatment outcomes of such diseases. The rising knowledge of dentist and growing consciousness of oral health, gives a hope that these goals might be fulfilled in the near future.

Table 1: Correlation of clinical finding and colposcopic findings over histopathological evaluation

Examination		Histopathology						
		Positive	Negative	Total	Senstivity	Specificity	PPV	NPV
Clinical	Positive 08	04	04	08	28.57	75.00	50.00	54.55
	Negative 22	10	12	22				
	Total 30	14	16	30				
Colposcopic	Positive 10	09	01	10	64.29	93.75	90.00	75.00
	Negative 20	05	15	20				
	Total 30	22	08	30				

PPV= Positive Predictive Value NPV = Negetive Predictive Value

Table 2: Vascular pattern seen in patients based on Colposcopic criteria

Clinical Lesion		Vascular pattern				
		Hair pin capillary pattern	Net-work capillary pattern	Punctation vessel pattern	Mosaic pattern	Atypical vessel pattern
Oral Leukoplakia	10	4	2	2	2	0
Oral submucous fibrosis	10	5	3	2	0	0
Oral Lichen Planus	6	2	3	0	1	0
OSCC	4	0	0	0	1	3
Normal oral mucosa	15	7	8	0	0	0

Table 3: Percentage of patients diagnosd correctly following clinical criteria and colposcopic technique

Clinical Lesion	Method	Total	Patients diagnosed correctly	% of Patients diagnosed correctly
Oral Leukoplakia	Clinical	10	5	50
	Colposcopic	10	8	80
Oral submucous fibrosis	Clinical	10	4	40
	Colposcopic	10	7	70
Oral Lichen Planus	Clinical	6	3	50
	Colposcopic	6	5	83.33
Oral squamous cell carcinoma	Clinical	4	3	75
	Colposcopic	4	4	100

IMAGES

FIG1: COLPOSCOPE AND STAINING SOLUTIONS USED.

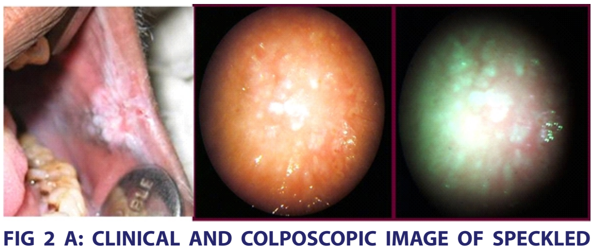

FIG 2 A: CLINICAL AND COLPOSCOPIC IMAGE OF SPECKLED LEUKOPLAKIA.

FIG 2 B: CLINICAL AND COLPOSCOPIC IMAGE OF EROSIVE LICHEN PLANUS.

FIG 2 C: CLINICAL AND COLPOSCOPIC IMAGE OF SQUAMOUS CELL CARCINOMA.

REFFRENCES

1. Epstein JB, Gorsky M, Cabay RJ, Day T, Gonsalves W. Screening for and diagnosis of oral premalignant lesions and oropharyngeal squamous cell carcinoma. Can Fam Physician 2008; 54: 870-5.
2. Silverman S Jr. Oral cancer, 5th ed. Hamilton, Canada: BC Decker, 2003.
3. Ravi Mehrotra, Sanjay Mishra, Mamta Singh and Mangal Singh. The efficacy of oral brush biopsy with computerassisted analysis in identifying precancerous and cancerous lesions. Head & Neck Oncology 2011; 2-7.
4. Paymaster JC. Some observations in oral and pharyngeal carcinomas in the state of Bombay. Cancer1962;15:578-83.
5. Kujan O, Glenny AN, Duxbury J, Thakker N, Sloan P. Evaluation of screening strategies for improving oral cancer mortality: a Cochrane systematic review. J Dent Edu 2005;69(2):255-64.
6. Kolstad P. Terminology and definitions. In: Kolstad P,editor. Atlas of colposcopy, 3rd ed. London: Churchill Livingstone 1982:21-31.
7. L' Estrange P, Bevenius J, Williams L. Intra oral application of micro-colposcopy: A new technique for clinical examination of oral tissue at high magnification. Oral Surg Oral Med Oral Pathol 1989;67:282-5.
8. Kirkup W, Singer A, Hill SA. The accuracy of colposcopically directed biopsy in patients with suspected intra-epithelial neoplasia of the cervix. Br J Obstet Gynecol 1980;87(1):1-4.
9. Helmerhorst TJM, Dijkhuizen GH, Calame JJ, Kwikkel HJ, Stolk JG. The accuracy of colposcopically directed biopsy in diagnosis of CIN. Eur J Obstet Gynecol Reprod Biol 1987;24(3):221-9.
10. Kamarthi Nagaraju, Shiva Prasad, L Ashok. Diagnostic efficiency of toluidine blue with Lugol's iodine in oral premalignant and malignant lesions. 2010;21(2):218- 23.
11. Disaia PJ, Creasman WT. Clinical Gynecologic oncology: Colposcopy. 1982.
12. Sehgal A, Murthy NS, Satyanarayana L, Singh V, Luthra UK. Small family norm and uterine cervical cancer. Acta Obstet Gynecol Scand. 1989; 68: 527- 528.
13. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med 2007; 36: 575–80.
14. Rajendran R. Benign & malignant tumors of oral cavity In. A textbook of Oral Pathology by Shafer WG, Hine MK, Levy BM. 5th ed. New Delhi: Elsevier India Private Limited; 2006. p. 121-149.
15. Martin IC, Kerawala CJ, Reed M. The application of toluidine blue as a diagnostic adjunct in the detection of epithelial dysplasia. Oral Surg Oral Med Oral Pathol Oral RadiolEndod. 1998;85:444-46.
16. Folsom TC, White CR, Bromer L. Oral exfoliative cytology: Review of the literature and report of a 3-year study. Surgery. 1972;33:61-74.
17. Epstein JB, Silverman S, Epstein JD, Lonky SA, Bride MA. Analysis of oral lesion biopsies identified and evaluated by visualexamination, chemiluminescence and toluidine blue. Oral Oncol. 2008;44:538-44.
18. Wang CY, Chiang HK, Chen CT, Chiang CP, Kuo YS, Chow SN. Diagnosis of oral cancer by light induced autofluorescence spectroscopy using double excitation wavelengths. Oral Oncology 1999;35(2):144-50.
19. Principles and practices of Colposcopy – Patrick Walker 2nd ed. B. Shakuntala Baliga. (Page No-1).
20. Gynther GW, Rozell B, Heimdahl A. Direct oral microscopy and its value in diagnosing mucosal lesion. Oral Surg Oral Med Oral Pathol. 2000;90:164-70.
21. Sankaranarayanan R, Wesley R, Thara S, Dhakad N, Chandralekha B, Sebastian P, et al. test characteristics of visual inspection with 4% acetic acid (VIA) and Lugol's iodine (VILI) in cervical cancer screening in Kerala, India. Int J Cancer. 2003;106:404-08.
22. Sellors JW, Sankaranarayanan R. Colposcopy and treatment of cervical intraepithelial neoplasia: A beginner's manual. Lyon: International Agency for Research on Cancer; IARC press 2003 (10). p. 73.
23. Walker P, Dexeus S, De Palo G, Barrasso R, Campion M, Girardi F, et al. Nomenclature Committee of the International Federation for Cervical Pathology and Colposcopy. International terminology of Colposcopy: An updated report from the International Federation for Cervical Pathology and colpocsopy. Obstet Gynecol 2003;101:175-177.
24. 21. Shetty DC, Ahuja P, Taneja DK, Rathore AS, Chhina S, Ahuja US, et al. Relevance of tumor angiogenesis patterns as a diagnostic value and prognostic indicator in oral precancer and cancer. Vasc Health Risk Manag 2011;7:41-47.
25. Ohri N, Kapoor C, Mohemmed RP, Vaidya S. An update on intraoral application of colposcopy. J Oral Maxillofac Pathol 2014;18:403-410.
26. Schmitt A. Colposcopy detection of atypical and cancerous lesions of the cervix. Obstet Gynecol. 1959; 13: 665-671.
27. Rene Cartier. Practical Colposcopy. Karger S, editor. 1977.
28. Marlow John. Colposcopy: Gynecologic oncology. Me Gowan L, editor. 1979.
29. Rosin MP, Poh CF, Guillard M, Williams PM, Zhang L, Macaulay C. Visualization and other emergingtechnologies as change makers for oral cancer prevention. Ann NY Acad Sci 2007;1098:167-83.
30. Coppleson M. The value of colposcopy in the detection of preclinical carcinoma of the cervix (Three years' experience at King George V Memorial Hospital, Sydney). J Obstet Gynaecol Br Emp. 1960; 67: 11-23.
31. Shetty DC, Ahuja P, Rathore AS, Ahuja US, Kumar K, Ahuja A, et al. Relevance of tumor angiogenesis patterns as a diagnostic value and prognostic indicator in oral pre-cancer and cancer. Vasc Health Risk Manag 2011;7:41-7.