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Use of Lugol's Iodine Solution in Screening of Oral Premalignant and Malignant Lesions

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Abstract: Background: This study also will help to identify the specific site of biopsy of oral pre-malignant and malignant lesions and to correlate lugol's iodine solution staining of oral tissue with histological findings. Objective: The aim of this study to detect any suspicious of oral cancerous and pre-cancerous lesions as an early diagnostic tool. Methods: Sixty cases of oral lesions were selected irrespective of age, sex, religion or socioeconomic status of the patient considering the inclusion and exclusion criteria. Patient selection was based on history, clinical examination and oral ulcers that do not heal more than two weeks. After staining of oral ulcer by Lugol's iodine, histopathological examination was done from lightly staining area (Lugol's iodine positive area) and another was deeply brown staining area (Lugol's iodine negative area). Results: Out of 60 patients, 59(98.3%) patients were lightly stain, out of 59 patients, 35 were diagnosed as squamous cell carcinoma (34 squamous cell carcinoma and one verrucous carcinoma), 22(36.7%) patients were pre-malignant (17 leukoplakias, 4 oral lichen planus and one erythroplakia) and 2(3.3%) patients were others (one hyperplastic change and one normal oral epithelium).One patient was deeply brown stain which was histopathologically normal oral epithelium. According to early screening of oral pre malignant and malignant lesions by Lugol's iodine enhanced attention of the clinician to a suspicious site of malignant and pre-malignant lesions in oral cavity. Conclusion: Lugol's iodine staining is more accurate than clinical or visual diagnosis.

Keywords: Lugol's Iodine, Early Screening, Oral Premalignant, Malignant Lesions

1. Introduction

Oral squamous cell carcinoma is one of the most common malignancies in the world with marked geographic incidences.[1] According to WHO report in 1983, Mouth cancer is the most common cancer in Southeast Asia.[2] There are 1.3 to 1.5 million cancer patients in Bangladesh, with about two lakh patients newly diagnosed with cancer each year. A report showing 85% of oral premalignant lesions may present leukoplakia. Leukoplakias examined microscopically may show hyperkeratosis with some degree of dysplasia in 20% of cases. Lesion of the tongue and floor of the mouth are likely to be dysplastic 25% and 20% respectively.[3]

Although Erythoplakia is rarely seen but 91% of erythoplakic lesions represent severe dysplasia or carcinoma.[4] Generally erythoplakia is seen in elderly male with the most common site being the lateral border of the tongue, floor of the mouth, soft palate and retromolar pad.[5]

Oral precancers associated with habits which occur in the oral cavity include leukoplakia and oral submucous fibrosis. 8-10% of these eventually progress to malignancy. Malignant transformation has been reported in 43% of dysplastic leukoplakia cases.[6] It is therefore important to identify these lesions early to enable management.

Visual examination continues to be a gold standard for the detection of early epithelial changes. The criteria for suspicion of oral premalignant and squamous cell carcinoma include changes in surface texture, loss of surface integrity, color, size, contour deviation or mobility of intraoral or extraoral structures. Oral carcinoma is usually first diagnosed when it becomes symptomatic and approximately two-thirds of the patients present with developed advanced disease, regional metastasis and consequently poor prognosis.[7]

Diagnostic aids can help the physician to decide whether the

suspicious lesion needs any clinical evidence of malignancy. In this situation even an expert eye may overlook malignant changes. Diagnostic aids can reveal these occult changes. In other word, diagnostic aids can be used as screening or as adjunctive tools.[8]

A number of techniques have been developed to supplement clinical examination and improve the diagnosis of early oral malignancy [7] They include (a) Toluidine blue staining test (b) Lugol's iodine (c) Methylene blue (d) Rose bengal (e) Oral exfoliative cytology (f) Brush biopsy (g) Chemiluminescent illumination.

No population-based screening programs for oral cancers have been implemented in developed countries, although opportunistic screening or screening as part of a periodic health examination has been advocated. There are different methods of screening for oral cancers. Oral cancer occurs in a region of the body that is generally accessible to physical examination by the patient, the dentist and the physician; and visual examination is the most common method used to detect visible lesions. Other methods have been used to augment clinical detection of oral lesions and include toluidine blue, brush biopsy, and fluorescence staining.[9]

The routine examination of asymptomatic and symptomatic patients can lead to detection of earlier stage cancers and premalignant lesions. There is no definitive evidence, however, to show that this screening can reduce oral cancer mortality, and there are no randomized controlled trials (RCT) in any Western or other low-risk populations.[10]

Techniques such as toluidine blue staining, lugol's iodine, brush biopsy/cytology, or fluorescence imaging as the primary screening tool or as an adjunct for screening have not been shown to have superior sensitivity and specificity for visual examination alone or to yield better health outcomes.[11]

The operating characteristics of the various techniques used as an adjunct to oral visual examination are not well established. Original Lugol's Iodine Solution consists 5g iodine and 10g Potassium iodide mixed with 85 ml distilled water to make a brown solution.[12] Use of Lugol's Iodine in early screening and also can be used to identify the lesion margin and extension in suspicious oral lesions. Tissue glycogen content is related to the degree of keratinization. Glycogen content is inversely proportional to the degree of keratinization because glycogen plays a key role in keratinization.[13]

Iodine staining method is highly effective for obtaining a clear boundary and distinguishing severity of dysplastic chance of suspicious lesion depending on the staining of Lugol's Solution.[14] The use of Lugol's Iodine Solution is limited to non-keratinized mucosa and also iodine staining cannot detect sub-epithelial in filtering tumors.[15]The iodine staining may be affected in oral cavity due to mucous composition of saliva. It is advisable to rinse with water and dry with gauze to avoid this problem. Lugol's Iodine is cheap, widely available, easy to use and only about 5 minutes are necessary to perform the staining procedure.[16] The study was conducted to diagnose the pre-malignant and malignant lesions in early stage and detection of the proper biopsy site on lesional mucosa, to evaluate the Lugol's iodine positive lesions histopathologically and to correlate Lugol's iodine solution staining of oral tissue with histological findings.

2. Materials and Methods

This is an observational study carried out in department of Oral and Maxillofacial surgery, Bnngabandhu Sheikh Mujib Medical University, Shahbagh, Dhaka from January 2011 to December 2012. Non-healing oral mucosal ulcers, red or white mucosal lesion more than 2 weeks were included in the study. Known case of oral carcinoma, lesion less than two weeks of duration, patients who have known history of allergy to iodine and non co-operative patient were excluded from the study. Sixty cases of oral premalignant and malignant lesions which were history and clinically diagnosed and were selected irrespective of age, gender, religion or socioeconomic status of the patient considering the inclusion and exclusion criteria. Data were processed and analyzed with SPSS-20. The test statistics used to analyze the data were descriptive statistics. The quantitative data were presented as mean and standard deviation from the mean. Sensitivity, accuracy, positive predictive value and negative predictive value were calculated according to standard formula from contingency table.

3. Results

Table I. *Age distribution of the study patients (n=60).*

Age	n	%
20-30	1	1.7
31-40	9	15.0
41-50	29	48.3
> 50	21	35.0
Mean±SD	50.4±10.1	
Range	30-80	

Number of the study patient was 60. Age range of the patient was 30 to80 years. The mean age of the patients was 50.4±10.1 years. Maximum patients 29(48.3%) were in 41-50 years age group.

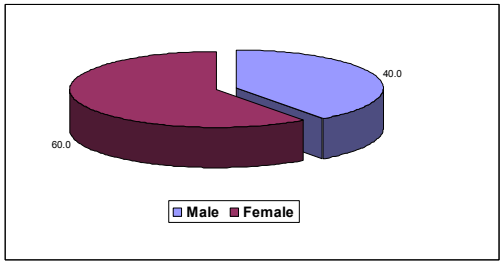

Figure 1. *Pie diagram showing the sex distribution of the study patients.*

Table II. *Distribution of the study patients according to site of lesion (n=60).*

Site of lesion	n	(%)
Buccal mucosa	49	81.6
Retromolar area	4	6.7
Alveolar mucosa	3	5.0
Tongue	3	5.0
Palatal mucosa	1	1.7

This study was carried out in 60 subjects. They were divided into male and female groups. Out of which 36(60.0%) were female and rest 24 (40.0%) were male patients.

Regarding the site of the lesion it was found that 49(81.6%) had buccal mucosa, 4(6.7%) had retro molar area, 3 (5.00%) had alveolar mucosa, 3(5.0%) had tongue and 1(1.7%) had palatal mucosa.

Table III. *Habit of the study patients (n=60).*

Habit	n	%
Betel quid with or without Chewing tobacco and smoking	44	73.4
Smoking only	12	20.0
Betel nut chewing only	2	3.3
No habitual history	2	3.3
Total	60	100.0

Regarding the habit of the patients, maximum 44(73.4%) patients had the habit of betel quid chewing with or without tobacco and smoking, 12(20.0%) smoking only, 2(3.3%) had the betel nut chewing only. Rest 2(3.3%) of the patients had no habitual history.

Table IV. *Distribution of the study patients according to screening with Lugol's iodine (n=60).*

Screening with Lugul's iodine	n	%
True Positive	57	95.0
True Negative	1	1.7
False positive	2	3.3
False Negative	0	0.0

According to screening with Lugul's iodine 57(95.0%) patients had true positive, 1(1.7%) patients had true negative, 2 (3.3%) patient had false positive and false negative had 0 (0.0%).

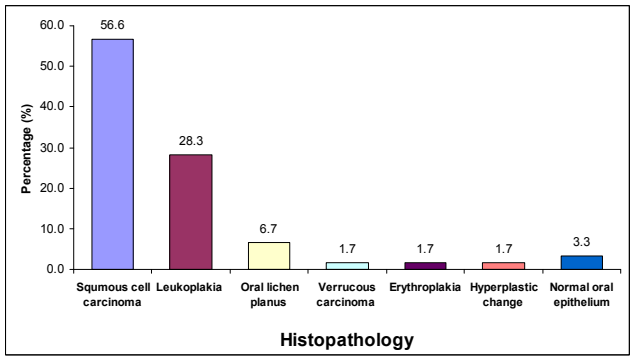

Figure 2. *Diagram showing distribution of the study patients according to histopathology (n=60).*

According to histopathological findings, squamous cell carcinoma 34(56.6%), Leukoplakia 17(28.3%), oral lichen planus 4(6.6%), normal oral epithelium 2(3.3%) and verrucous carcinoma, Erythroplakia, hyperplastic change, were 1(1.1%) in each type.

Table V. *Distribution of the study patient according to the stain positive (light stain or no stain) area and their histopathology.*

Stain Positive/ Negative	Malignant lesion No. (%)	Pre-malignant lesion No. (%)	Others No. (%)	Total No. (%)
Stain positive	35 (58.3%)	22 (36.7%)	2 (3.3%)	59 (98.3%)
Stain negative	0	0	1(1.7%)	1 (1.7%)

According to screening with Lugol's iodine in the low stain or no stain (stain positive) area of the lesion, 59 (98.3%) patients had stain positive. Out of 59 patients 35(58.3%) had malignant (34 squamous cell carcinoma and 1 verrucous carcinoma), 22 (36.7%) had pre-malignant (17 leukoplakia, 1 erythroplakia, 4 oral lichen planus) and 2(3.3%) others (1 hyperplastic change, 1 normal oral epithelium). 1(1.7%) patient had deeply brown stain (stain negative) which was normal oral epithelium.

Table VI. *Sensitivity specificity diagnostic accuracy positive and negative predictive values of the Screen test.*

	Malignant & Pre-malignant lesions
Sensitivity	100.0%
Specificity	33.3%
Diagnostic accuracy	96.6%
Positive predictive value	96.6%
Negative predictive value	100.0%

4. Discussion

In this study, we mentioned patients with oral mucosal lesions to test for association between Lugol's iodine staining outcomes as well as to clinicopathological correlations. Based on Lugol's iodine staining of the index lesions, the cases were classified finally positive and negative.

Age of patients has not played any role to detect significance of Lugol's iodine staining. But age is one of the etiological factors for oral malignant and premalignant lesions. In our study maximum 48.3% patients of 41-50 years age group were selected with mucosal ulcerations. No studies over these age groups are found.

Maeda K et al., (2009)[14] reported the result of such study, 65 patients study with Lugol's iodine and histopathological examination was done. Mean age were 59.2 years. Out of them 47.6% were male subject. In our study mean age were 50.4 and number of male were 24 (40.0%) patients out of 60 patients. Female were highest incidence in 36(60.0%).

A study in Southern India betel quid with tobacco and smoking were major independent risk factors of OSCC.[15] Another study reported betel chewing is the main etiological factor of OSCC in India; Pakistan & Srilanka.[16] Other risk factors shown or suggested for oral cancer include chewing of tobacco alone or in mixtures, poor oral hygiene and use of oral

prostheses.[17]

In this study, showed (Table-III) factor betel quid with and without tobacco chewing and smoking is major risk factors of oral squamous cell carcinoma that is 44(73.4%) and second height factor is the smoking 12(20.0%). It is completely different from the western world study which estimated the percentage of oral cancers attributable to cigarette smoking have been quite consistent, generally ranging from 75% to 90%.[18] This difference of habit may be due to social and religious.

A number of retrospective studies suggest that three clinical feature of malignant lesion and premalignant lesions are predictive of progressions for lesions; location of the lesion; size of the lesion and clinical appearance.[19]

In this study most common site is buccal mucosa 81.6% with the habit of betel quid without and with tobacco and smoking. A study showed that more common site is buccal mucosa. [20] Another study also showed that the most common site of OSCC was the buccal mucosa.[21] In this study, rest 4(6.7%) cases in retro molar area, 3(5.0%) cases in alveolar mucosa, 3(5.0%) cases in tongue and 1(1.7%) in palatal mucosa. We didn't detected size of the lesion and clinical appearance.

A study of 541 patients was screened in oral malignant and premalignant lesions. Out of 541 patients, 292 lesions (54%) were low stained. The histopathological examination of the 292 low stained lesion shows 79(27%) cases of oral squamous cell carcinoma,182(62.4%) cases of dysplasia of various degree, 2(0.7%) cases of lichen planus, 14(4.8%) cases of epithelial hyperplasia and in15(5.1%) cases the diagnosis were not specified.[22-25]

In present study, lesions details were as follows, squamous cell carcinoma 34(56.6%), Leukoplakia 17(28.3%), oral lichen planus 4(6.6%), normal oral epithelium 2(3.3%) and verrucous carcinoma, Erythroplakia, hyperplastic change was 1(1.1%) in each type.

Maeda K et al., (2009)[14] described effective staining method with iodine for leukoplakia and lesions surrounding squamous cell carcinomas of the tongue assessed by colorimetric analysis. They study 65 patients, out of them 57 patients were low stained. The histopathological diagnosis confirmed 23(40.4%) patients were mild epithelial dysplasia and 34(59.6%) patients were moderate to severe epithelial dysplasia. The rest of 8 patients which were deep stained, histologically confirmed 6 patients were normal epithelial mucosa and 2 were epithelial hyperplasia

In present study, 59 (98.3%) patients were staining positive. Out of 59 patients 35(58.3%) were malignant (34 squamous cell carcinoma and One verrucous carcinoma), 22 (36.7%) Patients were pre-malignant (17 leukoplakia, One erythroplakia, 4 oral lichen planus) and 2(3.3%) others (One hyperplastic change, One normal oral epithelium). 1(1.7%) patient was deeply brown stain (stain negative) which was normal oral epithelium.

Nagaraju et al., (2010)[26] described the diagnostic efficiency of Lugol's iodine in premalinant and malignant lesions. They studied 52 cases of patients, among the 52 cases stained positive in 51 cases and stain negative one case 51 cases were confirmed histologically as having dysplastic or carcinomatous changes while one case was confirmed histologically as benign lesion. The sensitivity was found to be 93% while the specificity was 80% and the positive predictive value and the negative predictive value 98% and 50%.The diagnostic accuracy of the stain was 92%.

Shiozaki et al.,(1990)[24] first described 20 years ago, the potential role of Lugol's iodine in oral squamous cell carcinoma detection.178 patients received screening for head and neck cancer. Among them 130 patients with oral cancer and dysplasia were identified within the screening program. The sensitivity was found to be 87.5% while the specificity was 84.2%.

Present study had measured sensitivity was 100%, accuracy 96.6%, specificity 33.3%, positive predictive value was 96.6% and negative predictive value of test was 100% of Lugol's iodine staining..

Kurita & Kurashina (1996)[15] studied that importance of Lugol's iodine in the delineation of the margins of dysplastic oral lesions. Out of 18 patients, 16 patients were positive results and only two patients were false positive confirmed histologically. The boundary of dysplastic or malignant epithelium was identified by iodine colour lining. They suggested a 5 mm border of normal tissue peripheral on the iodine positive area to completely remove the dysplastic epithelium.

McMahon et al. [16]evaluated in their comparative study, the efficacy of Lugol's iodine solution in the determination of extension of suspicious lesion. These authors demonstrated a significant less incidence of dysplasia or carcinoma among the margins of resection of lesion pre-stained with Lugol's solution. Mashberg [7] examined 105 oral lesions, result showed that 2% were false negative and 9.3% were false positive

In this study, 57(95.0%) patients are true positive, 1(1.7%) patient is true negative, 2(3.3%) patients are false positive .The two patients are false positive but before the application of Lugol's iodine clinically lesion like pre-malignant but after histological test lesions are benign and One patent is false negative 0(0.0%).

In contrast to other diagnostic procedures like brush cytology, which requires specimen collection and laboratory procedure, Lugol's iodine is a noninvasive method that provides real-time clinical information that may assist in completing a biopsy, biopsy site selection and referral. All the outcome of study variables supported by the series studies. By comparing our study results with above studies, we can reach to the conclusion that Lugol's iodine dye will increase attention of clinician to a suspicious site of malignant and premalignant lesion in oral cavity. Lugol's iodine staining is more accurate than clinical or visual diagnosis.

5. Conclusion

In conclusion, our opinion is that Lugol's iodine stain could be a useful aid when the clinical examination shows obvious

lessons in order to establish whether the lesions are at high risk of progression and to contribute to an early diagnosis of oral malignancy.

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