Early Detection of Cervical Cancer Through Acetic Acid Application – An Aided Visual Inspection

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ABSTRACT

Objective: To assess the sensitivity and specificity of visual inspection of cervix for detection of precancerous and early cancerous lesions of cervix.

Methods: In a Maternal and Child Health Care setting of New Delhi women underwent a detailed pelvic examination, visual inspection of cervix after 5% acetic acid application, cytology (pap smear), detailed colposcopic examination and colposcopic directed biopsy when indicated.

Results: Findings of aided visual inspection using 5% acetic acid and of cytology were evaluated among symptomatic 402 women against colposcopic findings and/or histologic reports. Seventy-three mild dysplasias, 50 moderate dysplasias, 45 severe dysplasias/Carcinoma in-situ and 40 early invasive cancerous cases were diagnosed histologically. The sensitivity of cytology (75.3%) was higher compared to that of acetic acid application (52.0%) for mild dysplasias. On the other hand, the sensitivity for detecting moderate dysplasias was 78% for cytology and 81.6% for acetic acid; for severe dysplasias/carcinoma in-situ it was 73.3% for cytology and 86.7% for acetic acid. For invasive cancers sensitivity for acetic acid application and cytology (95% for both modalities) was comparable. The specificity of cytology (99%) was higher compared to that of acetic acid application (94.3%). The false positive rate for cytology was 1.0% as against 5.7% for acetic acid application. The results of acetic acid application also showed a remarkable improvement in the sensitivity of unaided visual inspection for early cancerous lesion which was about 60% for early cancerous lesion and only 12% for mild dysplastic and 20% for moderate and severe dysplastic lesions in our earlier experience. It also reduced the false positive rates from 12% by unaided visual inspection to 5.7% by acetic acid application. Furthermore, cost of detection of one true lesion through acetic acid application (Rs.1689.00) was much lower as compared to the cost involved in cytology detected true lesions (Rs.2227.00). Visual inspection without acetic acid incurred Rs.6608.60 for detection of true lesion.

Conclusion: Screening for cervical precancerous and cancerous lesions using visual inspection aided by acetic acid may be a suitable low-cost and a feasible alternative modality for control of cervical cancer in a resource poor setting.

Keywords: Visual Inspection, Aided visual inspection, Acetic acid application

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INTRODUCTION

Cervical cancer is the leading malignancy among Indian women. It is estimated that every year about 90,000 new cases arise. In the absence of any screening program, most of these women come to the doctor at an advanced stage when hardly any curative management can be offered. In one of the World Bank reports, it is mentioned that women with cervical cancer lose about 18 years of their life. In the western countries, cervical cancer incidence and deaths have been brought under control using organised cytology screening programs. In developing countries, including India, due to other compelling health problems especially control of infectious diseases and population explosion, it is not possible to launch nationwide cytology screening programs for cervical cancer. Further, it was estimated in 1985 that if we increase trained manpower in the field of cytology by 12-fold, it will not be possible to screen more than one-third of eligible population (above 35 years of age) by 2000 A.D. As a result of these severe limitations, World Health Organisation suggested to use alternative strategies, like visual inspection of cervix for the control of cervical cancer[1]. We initially conducted visual inspection screening WITHOUT USING ACETIC ACID in Delhi in about 44,000 women[2]. In that study certain high risk clinical signs were identified (Unhealthy cervix, bleeding ectopies, and suspicious

Table 1. Percentage detection of different lesions by two screening modalities.

Detection modalities	Negative (n=194)*	Mild Dysp.** (n=73)	Moderate** Dysp. (n=50)	Severe** Dysp. (n=45)	Early** invasive CIS (n=40)	Positive Predictive value	Negative Predictive value
Acetic acid	183 94.3%	38 52.0%	41 81.6%	39 86.7%	38 95.0%	93.4%	77.9%
Cytology	192 99.0%	55 75.3%	39 78.0%	33 73.3%	38 95.0%	98.8%	83.8%

* Percentages indicate specificity
** Percentages indicate sensitivity

looking cervix). These high risk signs identified about 60% of cervical cancer in early clinical stages. This was in sharp contrast to the detection of cervical cancer in the "Cancer Clinic" where less than 5% women report at such an early stage. This technique, however, picked up about 12% false positive results i.e. identify a case as cancer when in fact it is not. Moreover, the pickup rate of precancerous lesions was as low as 12 to 20% depending on the severity of dysplasia.

Thus, there was a distinct need to improve the sensitivity and specificity of visual inspection. Towards this end different investigators are working out many newer approaches. One of these approaches is the use of magnifying device, the other being the application of acetic acid. Recently, few studies have been published regarding screening of women using acetic acid application (VIA). In one of these studies[3] (from Zimbave) it was reported that sensitivity of acetic acid application was 76.7%, but specificity was only 64%. However, the other study from India, reported a very high specificity (92.3%) and sensitivity (90.0%) for VIA[4]. We initiated this work with the main objective to assess whether the aided visual inspection using acetic acid could be used as an alternative modality to cytology to detect early cervical cancerous and precancerous lesions.

METHODOLOGY

Women attending Maternal Child Health (MCH) clinic with symptoms such as abnormal vaginal discharge, contact bleeding or irregular vaginal bleeding were referred to one of us (Veena Singh). A detailed pelvic examination, visual inspection of cervix after 5% acetic acid application, detailed colposcopic examination and colposcopic-directed biopsy was carried out as and when indicated. The results of cytology examination and visual inspection of cervix after acetic acid application were compared with colposcopic and/or histologic diagnosis. A test after acetic acid application was considered positive if the cervical epithelium becomes white and opaque with distinct margin within the transformation zone. The colposcopic examination was done in all patients irrespective of the results of the two screening procedures. Biopsy, however was done in only those patients (n=247) where colposcopic abnormalities were discovered. The colposcopic/histodiagnosis was considered as gold standard against which the sensitivity and specificity of cytology and acetic acid application were evaluated using standard statistical methods.

RESULTS

The mean age of the patients was 37.1 (±10.3) years and mean parity was 3.2 (±1.7) A total of 402 women were referred for detailed examination. Histologic examination revealed 73 mild dysplasias, 50 moderate dysplasias, 45 severe dysplasias/CIS and 40 invasive cancers. Detailed clinical examination of invasive cancer cases revealed that all of them were in stage IA and IB. The corresponding findings of cytology and of acetic acid application are given in Table I.

It could be seen that the sensitivity of cytology (75.3%) was higher as compared to that of acetic acid application (52.0%) for biopsy confirmed mild dysplasias. On the other hand, the sensitivity for detecting biopsy proven moderate dysplasias (78.0% vs. 81.6%) was equal. For severe dysplasias/CIS, sensitivity of acetic acid (86.7%) was superior to that of cytology (73.3%). For early invasive cancers sensitivity (95.0% vs. 95.0%) of acetic acid application and cytology was comparable.

In order to find out the false positive rates of cytology and of acetic acid application, we calculated the positively detected cases by the two techniques among women whose colposcopic or histologic examination showed normal results. The false positive rate for cytology was 1.0% as against 5.7% by acetic acid application. The specificity of cytology (99%) was superior to that of acetic acid application (94.3%). The positive predictive value of cytology was 98.8% and that of acetic acid application 93.4%. Negative predictive value of cytology was 83.8% and that of acetic acid 77.9%.

Earlier our experience[2] has shown that sensitivity of detecting early cancer was only 60% by visual inspection without using acetic acid. On the other hand, only 12% of mild dysplasia and 20% of moderate and severe dysplasias could be detected. The rate of false positivity was found to be 12%. Specificity of this screening modality was 88%.

Table II. Detection of a true lesion in 100,000 population by visual inspection, cytology and aided visual inspection (with acetic acid).

Detection modalities	Mild Dysp.	Moderate Dysp.	Severe Dysp.	CIS/ Invasive cancer	Total	False +ve lesion	Total test +ve lesion	Cost of screening (in thousands)	Cost of detection of truly positive lesion
Biopsy Diagnosis	1770	699	228	303	3000	-	-		
Visual* Inspection	212	140	46	182	580	11640	12220	Rs.2000	Rs.6608.60
Cytology**	1333	545	167	288	2333	970	3303	Rs.4700	Rs.2227
Aided*** Visual Inspection	920	573	187	288	1968	5529	7497	Rs.2200	Rs.1690

* Cost of screening + cost of biopsy (@ Rs.150 per case) = Rs.2,000,000 + 12220 X 150 = Rs.3,833,000
** Cost of screening + cost of biopsy (@Rs. 150 per case) = Rs.4,700.000 + 3303 X 150 = Rs.5,195,450
*** Cost of screening + cost of biopsy (@ Rs. 150 per case) = Rs.2,200,000 + 7497 X 150 = Rs. 3,324,550

In order to assess the relative performance of acetic acid application compared to cytology (the standard accepted screening tool) and to evaluate its efficacy against visual inspection (without acetic acid application), we attempted to compute the detection rates of precancerous and cancerous lesions using aided visual inspection, unaided visual inspection and of cytology in a hypothetical population of 100,000 women. It was further presumed that true prevalence of precancerous and cancerous lesions was 3% in this population (a prevalence close to Indian situation). The relative proportions of different grades of lesions were 59% for mild, 23.3% moderate, 7.6% severe and 10.1% CIS/invasive cancers. These proportions were derived from our previous cytology screening program (Annual Report, ICPO 1986-87). The results are given in Table II. It could be seen that cytology screening will pickup 2333 (77.7%) of the 3000 true lesions. In addition, 970 false positive lesions will also be picked up. Thus, through cytology screening program, a total of 3303 women need to undergo biopsy of which 970 (29.3%) would be unnecessarily biopsied. The cost of one pap smear in India has been estimated to be Rs.47.00 and that of biopsy Rs.150.00. Thus, the total cost of 100,000 women undergoing cytology screening will be Rs.4,700,000.00 and that of 3303 undergoing biopsy will be Rs.495,450.00. Thus it will incur a total cost of Rs.5,195,450.00 and the cost of detecting one true lesion through cytology will be Rs.2,227.00.

Visual inspection without acetic acid application will detect only 580 (19.3%) of the 3000 true lesions. The false positivity of visual inspection being 12%, a total of 11640 false positives (i.e. 12% of 97000 women without a true lesion) will be picked up. Thus the screening modality will detect a total of 12220 lesions (580 true and 11640 false positives) that required to undergo for biopsy confirmation. Cost of screening using visual inspection without acetic acid is Rs.20.00 per person. Thus Rs.2,000,000 will be needed to screen 100,000 women. In addition 12220 women need to undergo biopsy which require a sum of Rs.1,833,000. Thus the total cost of the screening program will be Rs.3,833,000 for the detection of only 580 true lesions i.e. Rs.6,608.60 per true lesion detected.

On the other hand, application of acetic acid will detect up to 1968 of 3000 true lesions (65.6%). In addition, 5529 false positive lesions will also be detected giving a total of 7497 lesions. Thus, 5529 of 7497(73.8%) will be unnecessarily biopsied because of a high rate of false positives. Considering cost of Rs.22.00 per women for screening with acetic acid, a total of Rs.2,200,000.00 will be needed for screening. Considering Rs.150.00 for one biopsy a total of Rs.1,124,550.00 will be required for biopsy. A total cost Rs.3,324,550.00 for screening with acetic acid application and biopsy for detecting 1968 true lesions will be needed. Thus, the total cost of detecting one true lesion by acetic acid application (Rs.1,690.00) was lower as compared to the comparative cost by cytology screening (Rs.2,227.00) or by visual inspection without acetic acid application (Rs.6,608.60).

DISCUSSION

The study was initiated with the main objective to consider whether the aided visual inspection could be used as an alternative modality to detect early cervical cancerous and precancerous lesions.

Earlier, it was shown that unaided visual inspection could detect about 60% of women with early cancers. The cancer indicators were cervical ectopy that bleeds when touched, small growths and suspicious unhealthy cervix[2,5]. The major drawback, however, was that it missed most of the precancerous conditions. The sensitivity to pickup early cancerous lesions was almost 60.0% of that of cytology screening and about 12.0% of women had false positive results. Our results of use of acetic acid application revealed improvement in sensitivity for detecting early cancerous lesions (95%) as compared to the detection rate of 60.0% by unaided

visual inspection. It was further noticed that there was a reduction in the false positive tests with the use of acetic acid application (5.7% only) as compared to unaided visual inspection (12.0%).

In addition, through use of acetic acid 52.0% of mild dysplasias, 81.6% of moderate dysplasia and 86.7% severe dysplasia/CIS could be detected where as unaided visual inspection missed most of the precancerous lesions (for example pick-up rate about 12.0-20.0% only). Thus, use of acetic acid remarkably increased the sensitivity of detecting not only invasive cancer but also of the precancerous lesions. It also successfully reduced the false positive rate.

White epithelium is a basic clinical appearance of the abnormal transformation zone and is due to osmolar change due to acetic acid application that causes water to leave the cell after which the cell membrane collapses around the abnormal and enlarged nucleus[6]. Thus, light transmission is interrupted and the lesion appears white. Acetic acid application is also done in colposcopy, where 10-12% false positive results are normally detected. A lower rate of false positive test in the present study may be due to the fact that no magnification was used which might have failed to detect certain benign aceto-white cervical lesions. Comparison of the results of acetic acid application with that of cytology clearly shows that the sensitivity of the two techniques was comparable for higher grade of lesions. Though the sensitivity of this technique was less for the detection of mild dysplasias, this may not be a serious limitation as most of the mild dysplasias tend to regress even without treatment. In our experience the progression potential of mild dysplasia was 10.0% only as compared to 25.0% progression of moderate dysplasia and 50% of severe dysplasias[7].

Though this study was undertaken in a setting where women with specific symptoms were referred for further evaluation, its results of sensitivity and specificity would be valid and applicable to other populations also as these two parameters of a screening test do not change in different clinico-epidemiologic setting[8]. However, predictive values would vary among different populations depending upon the prevalence of precancerous and cancerous lesions. Thus, in order to access the relative performance of visual inspection using acetic acid compared to cytology and visual inspection without the use of acetic acid, the results of sensitivity and specificity of different screening tests were computed in a hypothetical population of 100,000 women with 3% prevalence of precancerous and cancerous lesions. Since in India, the true prevalence of these lesions is around 3-4%, this exercise gives us realistic estimates of relative performance of different screening methods in our population.

Our results of screening by these modalities in a hypothetical 100,000 women population reveals that while acetic-acid would be about 84% as sensitive as cytology in picking up the true lesion (biopsy-proved), the cost of detection of one true lesion by acetic acid screening will be much less (Rs.1,689.00) as compared to the cost involved in detecting one true lesion by cytology (Rs.2,227.00). Even the recent publication in Lancet from Zimbabwe also found this technique more cost effective. When we compared with the cost of detecting true lesion using acetic acid screening with that of unaided visual inspection without using acetic acid, there was a tremendous improvement in cost considerations i.e. cost of detecting one true lesion dropped from Rs.6,608.60 to only Rs.1,690 by the addition of acetic acid application to visual inspection. Even, if the total cost of three programs is to be considered one gets lot of saving using acetic acid (Rs.3,324,550) when compared to unaided visual inspection (Rs.3,833,000) and cytology (Rs.519,540).

Recently, a question has been raised whether alternative screening strategies could be implemented on a wide-scale[9]. In view of the paucity of trained manpower in the field of cytology, lack of central cytology laboratories, loss of follow-up of women after cytology test, higher cost of detection of true lesions on one side and the relative ease of doing acetic acid application, lower cost involvement in biopsying and treating the patient in same setup during the same visit may make screening by acetic acid application a suitable alternative in resource poor settings.

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