Original Article

Visual inspection of cervix with acetic acid as a feasible screening test for cervical neoplasia among women attending at OPD in Rajshahi Medical College Hospital

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Abstract

Background: *Visual inspection of cervix after application of 3-5% acetic acid (VIA) is a potential alternative to Pap smear cytology for screening of cervical cancer in resource poor settings.* ***Objectives:*** *This study was to evaluate the performance of visual inspection based screening approach in the detection of precancerous and early cancerous lesions of the cervix.* ***Materials & Methods:*** *VIA was carried out in 540 eligible women attending Gynae OPD. Detection of well-defined, opaque, acetowhite lesion close to squamocolumnar junction or in transitional zone of the cervix constituted positive VIA. All screened women evaluated by colposcopy and biopsy were taken from colposcopically suspected areas. The final diagnosis was based on histology.* ***Results:*** *Out of 540 patients, 328 were VIA negative and 212 were VIA positive. Colposcopy showed normal results in 340 cases, low grade CIN in 138 cases, high grade CIN in 44 cases and cancer in 18 cases. There were biopsy proven chronic cervicitis and metaplastic changes in 423 cases, CIN I in 66 cases, CIN II in 25 cases, CIN III / carcinoma-in-situ in 5 cases. The sensitivity of VIA was 74.36%, specificity 70.45%, positive predictive value 41.04%, & negative predictive value 90.85%.* ***Conclusion:*** *VIA can differentiate a normal cervix from a precancerous cervix with reasonable accuracy. As it is low cost and simple method, it can be set in any hospital or any health care centre of rural or urban areas of poor resource settings.*

Keywords: *Cervical cancer screening, CIN, Pap's smear, VIA.*

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Introduction

Cervical cancer is the second most prevalent cancer among women world wide, accounting for nearly 452000 new cases per year.[1] Though no reliable statistical data about cancer is available, it is proved that cervical cancer is the most common cancer among women in Bangladesh and has annual incidence nearly 11956 which constitutes about 22-29% of the female cancers in different areas of the country.[2,3] All the tertiary level hospitals and institutes of this country are carrying a large load of cervical cancer patients because most of the cervical cancers are diagnosed at the advanced stage. The problem in our country is particularly acute because of poverty, early marriage, multiple marriage, high parity, poor nutrition, illiteracy and lack of basic knowledge about health matters. In several western countries, where screening programs have well established, cervical cancer rates have been decreased by as much as 65% over the past four decades[4], there has been no such trend in developing countries and in these countries, no clinically significant reduction in the incidence of cervical cancer has occurred. Screening programs were implemented in developing countries since the early 1980's, yet have failed to reduce the mortality rates. The WHO in 2002 estimated that only 5% of women in developing countries are screened appropriately[5]. Likely reasons for failure in screening programs include lack of funding, insufficient access in rural areas where most of the population in developing countries reside, lack of awareness/education as to need for screening, and poor follow-up. About 50% of all cancers occur in developing countries, yet only 5% of resources are spent on the fight against cancer worldwide.[6]

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Cervical cancer is preceded by a long phase of premalignant condition known as cervical intraepithelial neoplasia (CIN), usually occurs in women under the age of 40. The goal of cervical cancer screening is the detection and treatment of precancer before cancer develops.[7] To detect cervical intraepithelial neoplasia grades 2 or 3 (CIN II / III), which are considered to be the true precancerous lesions, we need a well-implemented secondary prevention system that provides screening of all women at risk as well as treatment of detected abnormalities according to the local policy. The Papanicolaou (Pap) smear has been shown to be highly effective in developed countries that have widespread screening programs. Cytology based screening (Pap smear) is effective but costly, needs technical supports and good number of cytopathologists. Additionally, only a small percentage of women with positive Pap smears have diagnostic evaluation and treatment, because of the lack of health centers that are able to treat preinvasive lesions. These problems with Pap smears have stimulated research on alternative tests. Among them, one method, direct visualization with acetic acid (VIA) has gained popularity and proven itself in many clinical trials as an adequate alternative to Pap smears in developing countries.[8-10] VIA is an attractive alternative to Pap smears for its ease of use, low-cost and fewer physician visits. Currently, to do a Pap smear, the doctor requires a speculum, lamp, slide, cytobrush, microscope, pathologist and a 2-week or more follow-up visit. With VIA, any trained nurse or physician can do the test. Tools needed include a speculum, lamp, cotton swab, and acetic acid (vinegar); no pathologist is needed. In this process 5% acetic acid is applied to the cervix with a large cotton swab and left for 30-60 seconds, after which the cervix is visually examined with the naked eye. Pre-cancerous lesions, with a higher ratio of intracellular proteins, turn white when combined with acetic acid.

VIA has a potential advantage over traditional screening techniques in poorly-resourced locations as there is immediate feedback of test results to the patient and importantly, treatment can be provided immediately after the test. If the test is negative, the patient can be told immediately without having to return to the doctor for results. In rural areas where people travel hours for a doctors' visit, a screening method requiring fewer visits will have a much higher success rate. In Bangladesh, the Department of Obstetrics & Gynaecology, BSMMU, Dhaka with the support of UNFPA has started cervical cancer screening training program based on VIA since 2004. This training program is aimed at developing skills of health service providers so that they can screen cervical cancer and assist in managing all these cases in different Medical College Hospitals, District Hospitals (DHS), and Maternal & Child Welfare Centers (MCWCS). Cervical cancer screening program has started in Rajshahi Medical College Hospital since September 2005. This study was initiated with the main objective to evaluate VIA as a screening tool in detecting precancerous & early cancerous lesions of the cervix. This research work was approved by Ethical Review Committee of Research cell of Rajshahi Medical College, Rajshahi (ref. RMC/ER/2010-2013/01).

Materials & Methods

This prospective study was carried out in Gynae out patient department (OPD) of Rajshahi Medical College Hospital from July '08 to December '09. Married women above 30 years of age or women having marital life more than 10 years, women with suspected or known STI, clinically symptoms and signs suggestive of early cervical cancer (history of vaginal discharge, irregular per vaginal bleeding, post coital bleeding, post menopausal bleeding etc.) and patients with clinically unhealthy looking cervix attending Gynae OPD or Maternal & Child Health (MCH) clinics were referred to VIA Centre for screening. Unmarried women, menstruating women with heavy flow, women who were currently pregnant or who had a history of abnormal cytology, previous treatment for CIN or cancer, were excluded from the study. Inclusion criteria, exclusion criteria and all the necessary information & clinical data collected for each of the study patients were systematically recorded in a pre designed questionnaire sheet. After proper counseling, the patients were placed in lithotomy position. Cervices were exposed by Cusco's vaginal speculum. Any evidence of infection, ectopy, tumor, ulcer etc was checked. Then 5% acetic acid was applied to the cervix for 1 minute & inspection was done to see any acetowhite area around SCJ or in TZ. The criterion standard for our study was cervical biopsy. Colposcopic evaluation and biopsy were done on all patients. Standard colposcopic criteria were used with the exception that when there was a question of metaplasia versus low grade CIN, lesions were classified as low grade. If colposcopy showed no abnormality, biopsy were taken from different quadrants of the cervix. If there were acetowhite areas, biopsies were taken from those suspected areas.

The results of the test (either positive or negative) were discussed with the women & appropriate treatment offered after proper counseling. VIA negative patients were asked for repeat VIA after 3 years. All patients who tested positive for high grade lesions (CIN II / III) underwent LEEP under local anaesthhesia or cryotherapy as an outdoor procedure. The tissue obtained was sent for histopathologic evaluation. The lesions found mildly dysplastic or worse on histopathologic evaluation were considered true positive cases.

Data Analysis

All data were compiled and analyzed manually by preparing a master sheet. Statistical interpretations were done by using Statistical Package for the Social Science (SPSS) program software. Validity of the screening tests was determined by calculating the four indices of test validity such as sensitivity, specificity, positive predictive value and negative predictive value on the basis of histopathology as a gold standard.

Results

During the study period from July '08 to December'09, 540 women were evaluated who fulfilled the inclusion criteria and provided informed consent. Out of 540 patients screened, 328 (60.74%) were VIA negative, and 212 (39.27%) were VIA positive (Figure 1). Finding of VIA were evaluated against colposcopic findings and histological reports. Colposcopy yielded normal results in 340 (62.96%) cases, low grade CIN in 138 (25.56%) cases, CIN-II in 36 (6.67%), CIN-III in 8 (1.48%) cases and cancer in 18 (3.33%) cases (Figure 2). On histology, there were biopsy proven chronic cervicitis with metaplastic changes in 423 (78.33%) cases,

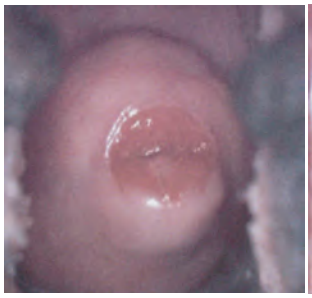

Fig. 1 VIA Negative

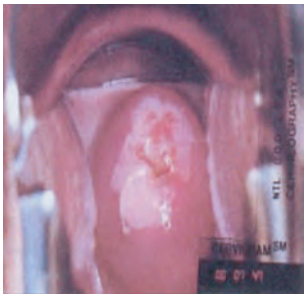

Fig. 2 VIA Positive

CIN-I in 66 (12.22%) cases, CIN-II in 25(4.62%) cases, CIN-III / carcinoma-in-situ in 5 (0.93%) cases. 18 cases of cervical carcinoma were diagnosed on VIA and colposcopy but ultimately 21 cases of invasive cancer were detected on histology. (Table I).

Table I: Percentage detection of different lesions by VIA, Colposcopy & Histopathology (n=540).

Screening results	VIA (n=540)	Colposcopy (n=540)	Histopathology (n=540)
Negative/ Normal/ Chronic cervicitis and metaplasia	328 (60.74%)	340 (62.96%)	423 (78.33 %)
CIN -I	150 (27.78 %)	138 (25.56%)	66 (12.22 %)
CIN -II	36 (6.67%)	36 (6.67%)	25 (4.62 %)
CIN -III/ Ca-in-situ	08 (1.48%)	08 (1.48 %)	05 (0.93 %)
Carcinoma cervix	18 (3.33%)	18 (3.33%)	21 (3.89 %)

Table I shows that out of 540 patients screened, 328 were VIA negative and 212 were VIA positive. Colposcopy yielded normal results in 340 cases, low grade CIN in 138 cases, high grade CIN in 44 cases and cancer in 18 cases. Of the 200 patients with white epithelium on colposcopy, 98 turned out to be negative on histology. There were biopsy proven chronic cervicitis and metaplastic changes in 423 cases, CIN I in 66 cases, CIN II in 25 cases, CIN III/ carcinoma-in-situ in 5 cases. 18 cases of cervical carcinoma were diagnosed on VIA and colposcopy but ultimately 21 cases of invasive cancer were detected on histology.

Table II: Screening results of VIA & Colposcopy

	VIA	Colposcopy
Sensitivity	87 of 117 (74.36%)	102 of 117 (87.18%)
Specificity	298 of 423 (70.45%)	325 of 423 (76.83%)
Positive predictive value (PPV)	87 of 212 (41.04%)	102 of 200 (51.0%)
Negative predictive value (NPV)	298 of 328 (90.85%)	325 of 340 (95.59%)

Sensitivity: is the tests ability to correctly identify those individuals who truly have the disease among the screened population. The closure the sensitivity is to 100%, the more likely that the patient has a disease. For VIA it is 74.36% and for colposcopy it is 87.18%. **Specificity:** is the tests ability to correctly identify those individuals who do not have the disease. The closure the specificity is to 100%, the more likely that the patient is truly disease free. For VIA it is 70.45% and for colposcopy it is 76.83%. **PPV:** is the tests ability to correctly identify those individuals who truly have the disease among all those individuals whose tests are positive. For VIA it is 41.04% and for colposcopy it is 51.0%. **NPV:** is the probability that the person with a negative test does not have the disease. For VIA it is 90.85% and for colposcopy it is 95.59%.

Table III: Screening results of VIA for different grades of CIN

	CIN-I	CIN-II	CIN-III
Sensitivity	50 of 63 (79.37%)	23 of 25 (92.0%)	5 of 5 (100%)
Specificity	315 of 477(66.04%)	326 of 515 (78.55%)	328 of 535 (61.31%)
PPV	50 of 212 (23.58%)	23 of 212 (10.85%)	5 of 212 (2.36%)
NPV	315 of 328 (95.26%)	326 of 328 (99.39%)	328 of 328 (100%)

Table III shows that sensitivity of VIA for CIN I, CIN II and CIN III are 79.37%, 92.0% and 100% respectively. Specificity of VIA for CIN I, CIN II and CIN III are 66.04%, 78.55% and 61.31% respectively. PPV of VIA for CIN I, CIN II and CIN III are 23.58%, 10.85% and 2.36% respectively. NPV of VIA for CIN I, CIN II and CIN III are 95.26%, 99.39% and 100% respectively.

Discussion

This study was conducted as part of our effort to evaluate the performance of visual inspection-based screening approaches in the detection of cervical lesions. A review of different studies in India indicated that a simple visual approach involving direct unmagnified inspection of the uterine cervix without acetic acid application ("down staging") was not satisfactory in the early detection of cervical carcinoma and precursor lesions.[11-14] It has both poor sensitivity and poor specificity in the detection of lesions, particularly preinvasive ones, because there is wide variability in the appearance of the cervix in a population in which obstetric trauma to the cervix is frequent, and in which cervical and vaginal infections are common. But various studies proved that visual inspection of the uterine cervix after the application of 3-5% freshly prepared acetic acid can lead to the satisfactory detection of cervical lesions and lesions missed by cervical cytology.[15-18] Since we screened a hospital- based symptomatic population, our VIA positivity rate was higher than that found in other studies. If this test had done among general population, we may have obtained lower positive rates. The sensitivity of VIA to detect mild dysplasia or worse, as shown in various studies, ranges from 63% to 77%[19-21]. In our study, the sensitivity of VIA to detect mild dysplasia was 79.37%. (Table III). There were 30 cases of biopsy proven high grade lesions (CIN II-25 & CIN III-5) and 28 of these were detected on VIA giving a high sensitivity rate ranging from 92-100% (for CIN II, sensitivity 92% & for CIN III, sensitivity 100%) and negative predictive value for CIN II- 99% and for CIN III-100%. (Table III). Only two cases of high grade lesions were missed as they had contact bleeding during VIA procedure. In our study VIA and biopsy correlation is poor for LSIL which resembles normal metaplastic epithelium on VIA as well as on colposcopy but the sensitivity and specificity increase in picking up HSIL which is indeed a true cancer precursor and early invasive cancer.

The specificity of VIA was 70.45%, positive predictive value was 41.04% and negative predictive value was 90.85%. The low sensitivity of VIA (74.36%) in our study could be due to light source which was not halogen-type and the low specificity (78.33%) could be due to a large number of inflammatory lesions which is responsible for a large number of false positive results. Our results are comparable to those of The University of Zimbabwe and Johns Hopkins study (76.7% and 64.1% respectively).[22] Shankaranarayanan[23] had published results from a randomized intervention trial in India comparing VIA to cytology and to HPV DNA testing and found that all three had similar detection rates of CIN-II and CIN-III lesions and the range of sensitivity for VIA was 67-79% and specificity 49-86%.

The findings of our study and results from previous investigations indicate that a major limitation of VIA is its low specificity (less than 80% in most of reported studies). This, inevitably, leads to high rates of referral and treatment, with the associated potential for increased patients' discomfort and increased numbers of side-effects. The positive predictive value we report for VIA is lower than that found by Shankaranarayanan et al[23]. This can most likely be explained by our institutional policies, which required us to diagnose any lesion suggesting CIN-I. Shankaranarayanan et al. considered as positive at VIA only those cases with a distinctive and clear acetowhite area, which is more likely to be related to CIN II/III. It seems from our study that colposcopic magnification associated with marginal improvement in sensitivity without gains in specificity. Nonetheless, our study shows that VIA can identify most true cases of cervical pre-cancer and cancer. Where large-scale Pap-smear screening is not now available and is not likely to be available consistently in the future, VIA could be a readily available, potentially sustainable means of testing that, when coupled effectively with treatment, could reduce the burden of disease in populations in which the incidence of cervical cancer is high. Even where cytology services are well established, VIA might be a cost-effective method of rapidly differentiating between a potentially diseased cervix and a healthy one. Test negative would be reassured that most probably they do not have HSIL or cancer. It is likely that standardized training, development of quality control procedures and uniform definitions of VIA test outcomes may contribute to some improvement of the specificity of visual inspection based screening approaches without substantially lowering sensitivity. Long term efficacy of VIA based screening in reducing the cervical cancer burden remains to be demonstrated.

The limitation of our study was that it did not reflect the susceptible women of whole community who should be screened as the centre still using an opportunistic approach. In any of the intervention districts in the country, there would be an average population of married women aged 30 and above of 360,000 and all of them should be screened under this programme.[24] The human and financial resources available in a country determine what screening tests are to be performed and who will perform them. Visual inspection is likely to assume a central role in prevention of cervical cancer in many parts of the world because it does not require technical supplies and it allows diagnosis and treatment at a single visit. The time has come, to integrate VIA based screening programme at the primary care level of health services and to downstage cancer cervix in our country.

Conclusion

From the present study finding it would be concluded that the benefits of low costs, ease of implementation and a point of care diagnosis and treatment algorithm, VIA can be used as a screening tool in rural areas and in hospitals, cancer institutes and health centers with better facilities. Results from ongoing studies will further clarify the role of VIA.

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