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Screening of Cervical Cancer by VIA among women in Rajshahi Medical College Hospital

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Abstract:

Introduction: *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. VIA has gained popularity and proven itself in many clinical trials as an adequate screening test. VIA is an attractive alternative to Pap smears for its ease of use, low-cost and fewer physician visits. Currently VIA is done in tertiary level hospitals by trained health care providers to generalize its efficacy.*

Objective*: The main objective of this study was to evaluate the efficacy of visual inspection based screening approach in the detection of precancerous & early cancerous lesions of the cervix.*

Materials and Methods: *This study was done as a part of an ongoing screening program in Rajshahi Medical College Hospital from July 2008 to December 2009. VIA was carried out in 540 eligible women attending Gynae OPD for gynecological problems. The women underwent a complete clinical evaluation. Detection of well-defined, opaque, acetowhite lesion close to squamocolumnar junction (SCJ) or in transitional zone (TZ), well-defined circumferential, acetowhite lesions or dense acetowhitening of ulceroproliferative growth on the cervix constituted a positive VIA. All screened women evaluated by colposcopy and biopsy were taken from colposcopically suspected areas or in cases of VIA negative from different quadrants of the cervix. The final diagnosis was based on histology, which allowed direct estimation of sensitivity, specificity, and predictive values of VIA. Those with CIN I or cancerous lesions diagnosed by histology were considered as true positive.*

Results: *Out of 540 patients screened, 328(61%) were VIA negative and 212(39%) were VIA positive. Out of positive cases 87 (41%)%) seemed to have pathology. Colposcopy yielded normal results in 340 (63%) cases, low grade CIN in 138 (26%) cases, high grade CIN in 44 (8%) cases and cancer in 18 (3%) cases making total 200 cases. Of the 200 (37%) patients with positive colposcopy, 98 (49%) turned out to be negative on histology. There were biopsy proven chronic cervicitis and metaplastic changes in 423 (78%) cases, CIN I in 66 (12%) cases, CIN II in 25 (5%) cases, CIN III/ carcinoma-in-situ in 5 (1%) cases. Eighteen (3%) cases of cervical carcinoma were diagnosed on colposcopy but ultimately 21(21%) cases of invasive cancer were detected on histology. The sensitivity of VIA for biopsy proven CIN I was 74.36%, specificity 75.8%, positive predictive value 41.04%, & negative predictive value 90.85%.*

Conclusion: *VIA can differentiate a normal cervix from a precancerous cervix with reasonable accuracy. Till now a good number of studies had been carried out in different countries of the world and now it is well established that the sensitivity of VIA equaled or exceeded the reported rates for conventional cervical cytology. 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.*

Key words*: Cervical cancer screening, Visual Inspection of Cervix with Acetic acid, Colposcopy, Cervical Intraepithelial Neoplasia, Histology.*

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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]

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 precancerous 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 & assist in managing all these cases in different Medical College Hospitals, District Hospitals, and Maternal & Child Welfare Centers.

As a part of this pilot program, cervical cancer screening program has started in Rajshahi Medical College Hospital since September 2005. This study

was initiated with the main objective to assess the efficacy of VIA as a screening tool to detect cancerous and precancerous 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 squamocolumner junction (SCJ) or in transformation zone (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 & 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.

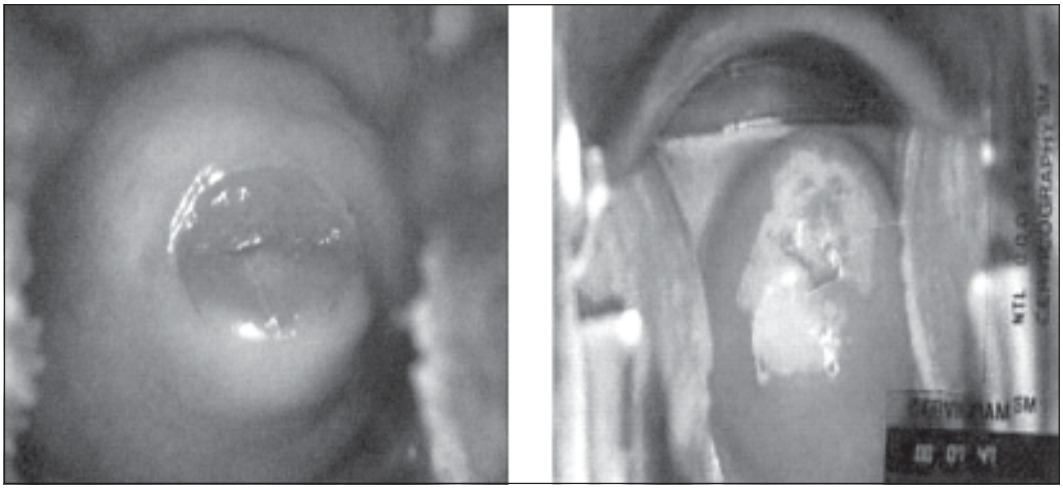
Study Results:

During the study period from July '08 to Dec'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 (Figure1). Out of positive cases 87 (41%) seemed to have pathology. 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 (Table 1).

On histology, there were biopsy proven chronic cervicitis with metaplastic changes in 423 (78.33%) cases, CIN-I in 66 (12.22%) cases, CIN-II in 25(4.62%) cases, CIN-III/ carcinoma-in-situ in 5 (0.93%) cases. Eighteen (3%) cases of cervical carcinoma were diagnosed on colposcopy but ultimately 21 cases of invasive cancer were detected on histology (Table 1).

The sensitivity of VIA for biopsy proven CIN I was 74.36%, specificity 75.8%, positive predictive value 41.04%, & negative predictive value 90.85%. On the other hand, out of 117 biopsies with positive results, 102 were detected on colposcopy giving a sensitivity of 87.18%, specificity 76.83%, positive predictive value 51.0%, & negative predictive value 95.59% respectively (Table 2).



VIA Negative *VIA Positive*

Table-I

Percentage detection of different lesions by Colposcopy & Histopathology.

Screening results	VIA (n=540)	Colposcopy (n=540)	Histopathology (n=540)
Negative/	328 (60.74%)		
Normal/		340 (62.96%)	
Chronic cervicitis and metaplasia			423 (78.33 %)
Positive	212 (39.27%)	200 (37.04%)	117 (21.67%)
CIN-I		138 (25.56%)	66 (12.22 %)
CIN-II		36 (6.67%)	25 (4.62 %)
CIN-III/ Ca-in-situ		08 (1.48 %)	05 (0.93 %)
Carcinoma cervix		18 (3.33%)	21 (3.89 %)

Table-II

Screening results of VIA & Colposcopy

	VIA	Colposcopy
Sensitivity[1]	87 of 117 (74.36%)	102 of 117 (87.18%)
Specificity[2]	298 of 393 (75.8%)	325 of 423 (76.83%)
Positive predictive value (PPV)[3]	87 of 212 (41.04%)	102 of 200 (51.0%)
Negative predictive value (NPV)[4]	298 of 328 (90.85%)	325 of 340 (95.59%)

[1]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.

[2] 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.

[3] PPV: is the tests ability to correctly identify those individuals who truly have the disease among all those individuals whose tests are positive.

[4] NPV: is the probability that the person with a negative test does not have the disease.

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%[19-23]. In our study, the sensitivity of VIA was 74.36%. (Table1). There were 30 cases of biopsy proven high grade lesions and 44 of these were detected on colposcopy giving a high sensitivity rate 77% and negative predictive value 96%**.** (Table2). 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 75.8%, positive predictive value was 41.04% & 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 & the low specificity (75.8%) 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 had published results from a randomized intervention trial in India comparing VIA to cytology & to HPV DNA testing & found that all three had similar detection rates of CIN-II & CIN-III lesions & the range of sensitivity for VIA was 67-79% & specificity 49-86%[23].

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. 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. 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 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:

Sensitivity of VIA is closer to specificity.

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