Research Article

Potential of visual inspection with acetic acid as a screening test in comparison to conventional papanicolaou smear in detection of colposcopic biopsy proven cervical intraepithelial neoplasia: A tertiary centre experience

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ABSTRACT

Background: Although it is well established that organized cytological screening programs are the mainstay for cancer cervix control but the financial and logistic burden of operating such a program is considerable. This has prompted the evaluation of alternative feasible techniques. Early and ongoing comparative studies worldwide showed visual inspection with acetic acid (VIA) as potential alternatives to cervical cytology because of their low cost, the ease of use, high sensitivity and immediate result allowing "see and treat" at first visit. **Objectives:** To evaluate the performance of VIA and its comparison with cytology in cervical cancer screening. **Materials and Methods:** A total of 400 non-pregnant reproductive age women were subjected to papanicolaou Pap smear) and VIA in this prospective study done in a tertiary-care centre in Delhi. Reference standard used for all was colposcopy and colposcopic-directed biopsy (when required). **Results:** Of 400 Pap smears done 11.75% were normal, 77.5% inflammatory, 5.5% had atypical squamous cells (ASC) atypical glandular cells of undetermined significance (AGUS), 0.25% ASC-H, 0.5% AGUS, 2% low-grade squamous intraepithelial lesions (LSIL), 1.5% high-grade squamous intraepithelial lesion (HSIL), and invasive cancer in 0.5%. With LSIL and above smears as significant, the sensitivity and specificity of Pap were 50% and 97.66%, respectively. VIA was positive according to two thresholds. When high-threshold was used then only well demarcated, opaque white areas near the squamocolumnar junction were taken as positive whereas in low-threshold criterion faint or ill-defined ace to white anywhere and well-defined areas away from squamocolumnar junction was also taken as positive. 29.3% were positive with low-threshold criterion for VIA and 9.3% with high-threshold criterion. The sensitivity with low-threshold criteria was 100% and specificity 72.7%. **Conclusion:** The sensitivity with low-threshold criteria was 100% and specificity 72.7%. With high-threshold sensitivity and specificity were 85.7% and 95%, respectively. **Conclusion:** VIA with low-threshold criteria had high sensitivity (100%), but specificity (72.7%) was low, but with high-threshold criteria for positivity, the specificity increases up to 95% which is comparable to cytology. The gynecologists in tertiary-care centers can use the high-threshold criterion effectively, and patient with significant lesions can be directly subjected to further treatment at the earliest thus reducing loss to follow-up.

KEY WORDS: Cervical Cancer; Screening; Colposcopy; Sensitivity; Specificity

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INTRODUCTION

As per population-based cancer registries in India, cervical carcinoma is the second most common cancer among women after breast cancer.[1] Majority (83%) of the cases occur in developing countries which possess only 5% of global resources.[2] India is a high-risk country for cervical cancer,

accounting for more than quarter (26.1-43.8%) of the world's burden.[3,4] However, the eradication of invasive cervical carcinoma is a realistic vision as the disease is preventable due to the long precancerous stage which if detected in time is amenable to treatment. Cervical cancer screening is acknowledged as currently the most effective approach for cervical cancer control but in developing countries cytology-based programs has failed to achieve major impact because the financial and logistical burden of operating such a program is considerable. Functional mass screening program is still in its early stage in our country.[5] The disadvantages of cytology-based screening programs are a high loss to follow-up, low coverage, technical manpower requirement and cost factor. In a recent study, Ashwini et al. found that 96.5% of respondent were not aware about screening for cervical cancer.[5] There is a clear need for viable, accurate and effective alternative screening method for control of cancer cervix in countries with limited resources. Based on several early and ongoing comparative studies worldwide visual inspection with acetic acid (VIA) and Lugol's iodine (VILI) are potential alternatives to cervical cytology because of their low cost, the ease of use, high sensitivity and immediate result allowing "see and treat" at first visit. There is a limited evaluation of VIA as a screening test in hospital setting - a well-equipped health care set up so that they can replace or supplement papanicolaou (Pap) smear as primary screening tests even where resources are adequate. In India, a test with better sensitivity is required as coverage is more important and multi-visit of patients is limited. If a potential alternative to cytology, such as VIA is chosen for screening, considerable attention should be given to the proper monitoring and evaluation of the program inputs and outcomes before further expansion. The present initiation was taken in view of the persistent high incidence and mortality of cervical cancer in India. It remains the most common cause of cancer in women here. As it was discovered that cervical cancer is a preventable disease due to its long natural course of progression, efforts were made to explore various screening tests. Now visual screening tests are being evaluated, and initial studies have found it to be feasible and acceptable. This study is an endeavor to address to these problems by assessing the performance of visual screening tests and exploring the possibility of using them as primary screening methods.

MATERIALS AND METHODS

This study was a hospital based non-randomized, analytical, descriptive, study. The women presenting to the gynecology outpatient department with various gynecological complaints were invited to participate in the study. Patients are having frank growth, postmenopausal, bleeding per vaginam, using intravaginal medications, those with prior hysterectomy and those who took prior treatment for cancer cervix or cervical intraepithelial neoplasia were excluded. 400 sexually active patients who presented to the gynecological outpatient department with various gynecological complaints were evaluated and according to the exclusion and inclusion criteria were enrolled in the study. The women who were eligible to participate and gave consent were thoroughly interviewed, histories were taken, and general physical examinations were done. Pap smear was first taken. Then, freshly prepared 5% acetic acid was applied on the cervix and findings were carefully observed and documented according to a high-threshold and low-threshold criteria of an international agency for research on cancer (IARC) separately.[6] Following the screening tests, each patient was subjected to colposcopy in colposcopy room. If colposcopy was suspicious, then only cervical biopsy was taken from the abnormal area/areas. In our study, no verification bias was there as all participants were subjected to diagnostic tests.

The reference standard for defining final disease status was a combination of colposcopy and biopsy.[7,8] Disease status was assessed based on histology if a biopsy was taken; if not, based on colposcopy. Reference standard negatives included women who were assessed as negative for suspicious lesions by colposcopy, as well as those who were assessed as positive by colposcopy, but negative by histology. True disease was defined as histologically confirmed cervical intraepithelial neoplasia 2 (CIN 2) or greater lesion. Cytology result was reported according to the Bethesda system by pathologist and VIA documented according to the IARC criteria. The compiled results were statistically analyzed applying Chi-square, paired *t*-test, and student's *t*-test. The sensitivity and specificity were calculated for each and comparison was done.

RESULTS

Table 1 summarized that majority were of age group 26-45 years (78.1%) and 17.5% were <26 years of age. The mean age of the study group was 33.91 ± 7.59 years. It varied from 19 to 52 years. Postmenopausal women were not included in the study as standard colposcopy is not reliable in them. The mean parity of women was 2.8 ± 1.47 ranging from 0 to 9. Majority (85.5%) of the patients was housewives and 92.5% were hindus. More than 50% were literate, only 8.3% were graduate or above. Illiterates also formed a significant part of the group. The bulk of the group (71.3%) was formed of patients from lower strata, and there was no patient from upper class in the study.

Table 2, a detailed correlation of the Pap smear report with a reference standard (colposcopy or biopsy) was done. Out of 400 Pap smears done 310 had an inflammatory report of which. Only 32 had suspicious colposcopy which when subjected to biopsy-chronic cervicitis was reported in 27 and CIN 2 in 5 patients. Of the 47 normal Pap reports only one had suspicious colposcopy which on biopsy revealed chronic

cervicitis. Among 22 atypical squamous cells of undetermined significance (ASCUS) 6 had suspicious colposcopy but only 2 had CIN 2 reported. No significant lesion was found with atypical glandular cells of undetermined significance (AGUS) or ASC-H on Pap. There were 8 Low-grade squamous intraepithelial lesion (LSIL) reported in the study group of which only two were colposcopically found suspicious. Out of these two, one had CIN 2. Out of the 6 high-grade squamous intraepithelial lesion (HSIL) reported 5 were colpscopically abnormal which were then subjected to biopsy. The results were CIN 2 IN two patients, CIN 3 in one and one had invasive cancer. Each case of squamous cell carcinoma and adenocarcinoma reported on Pap were confirmed on histological examination.

Table 1: Sociodemographic profile of patients (*n*=400)

Variables	Category	*n* (%)
Age group (years)	≤25	70 (17.5)
	26-35	171 (42.8)
	36-45	133 (35.2)
	45-55	28 (6.5)
Occupation	Housewife	342 (85.5)
	Laborer or servant	38 (9.5)
	Service or business or professional	20 (5.0)
Socioeconomic status	Lower	285 (71.3)
	Middle	115 (28.7)
Educational level	Illiterate	176 (44)
	Elementary level (I-V)	62 (15.5)
	Secondary level (VI-XII)	129 (32.3)
	Graduate and higher	33 (8.3)
Religion	Hindu	370 (92.5)
	Muslim and others	30 (7.5)

When detailed correlation of VIA with reference standard was done (Table 2), it was found that only 8 of the positive VIA patients had a normal colposcopy, the rest 29 had suspicious colposcopy which was subjected to biopsy. The biopsy reports were 1 unremarkable, 15 chronic cervicitis, 8 CIN 2, 1 CIN 3, 2 squamous cell carcinomas, and 1 adenocarcinoma. Similarly, comparison of low-threshold VIA positives with detailed biopsy report is as shown.

With LSIL and above smears were as positive, the sensitivity and specificity were 50% and 97.66%, respectively, while negative predictive value (NPV) and positive predictive value (PPV) were 98.1% and 43.75%, respectively, in the study.

Table 2: Distribution of Pap smear and VIA findings in relation to biopsy (*n*=400)

Pap smear	Colposcopy/biopsy (*n*=51)								
	Normal	Chronic cervicitis	Unremarkable	CIN 2	CIN 3	Sq. cell ca	Adeno-carcinoma	Granulomatous/TB	Total
Normal	46	1	3	0	0	0	0	0	48
Inflammation	281	34	0	5	0	0	0	0	310
ASCUS	16	4	0	2	0	0	0	0	22
ASC-H	1	0	0	0	0	0	0	0	1
AGUS	0	2	0	0	0	0	0	0	2
LSIL	6	1	0	1	0	0	0	0	8
HSIL	1	1	0	2	1	1	0	0	6
SQ cell Ca	0	0	0	0	0	1	0	0	1
Adeno Ca	0	0	0	0	0	0	1	0	1
Epithelioid granuloma	0	0	0	0	0	0	0	1	1
Total (%)	349	33		10	1	2	1	1	400
VIA (high)									
Negative	341	18	2	2	0	0	0	0	363
Positive	8	15	1	8	1	2	1	1	37
Total (%)	349	33	3	10	1	2	1	1	400
VIA (low)									
Negative	272	9	0	0	0	0	0	0	281
Positive	77	24	3	10	1	2	1	1	119
Total (%)	349	33	3	10	1	2	1	1	400

CIN: Cervical intraepithelial neoplasia, VIA: Visual inspection with acetic acid, TB: Tuberculosis, ASCUS: Atypical squamous cells of undetermined significance, AGUS: Atypical glandular cells of undetermined significance, HSIL: High-grade squamous intraepithelial lesion, LSIL: Low-grade squamous intraepithelial lesions, ASC: Atypical squamous cells

The results confirm the fact that cytology is a test with low sensitivity but very high specificity. The sensitivity of VIA with low-threshold criteria was 100% and specificity 72.7% in the study. When a high-threshold criterion was applied, the sensitivity and specificity were 85.7% and 95%, respectively (Table 3).

When the results of the Pap smear and VIA were compared, it was obvious that the sensitivity of VIA (85.7-100%) was quite high as compared to Pap (42.85-57.14%) what so ever threshold criterion was applied. Hence, in terms of sensitivity VIA should be preferred. But if high-threshold criterion is used, a high specificity (95.0%) can also be achieved that is comparable to that of Pap smear test (92.2-99.48%) (Table 4).

DISCUSSION

The mean age of the study group was 33.91 ± 7.59 years, and the majority was of age group 26-45 years (78.1%). The mean parity was 2.8 ± 1.47 ranging from 0 to 9. The age at first intercourse ranged from 13 to 33 years, mean being 17.88 ± 3.07 years. The most common complaint was white discharge per vaginam (29.3%). Next common complaints were lower abdominal pain, dyspareunia, and menstrual disturbances. The Pap smear was normal or negative smear in 11.75%, inflammation was reported in 77.5%, ASCUS in 5.5%, ASC-H in 0.25%, AGUS in 0.5%, LSIL in 2%, HSIL in 1.5%, and invasive cancer in 0.5%. In this study, VIA was reported to be positive according to two thresholds. When high-threshold was used then only well demarcated, opaque white areas near the squamocolumnar junction (SCJ) were taken as positive; whereas in low-threshold criterion faint or ill-defined acetowhite anywhere and well-defined areas away from SCJ were also taken as positive. Accordingly, the positivity rate of VIA with low-threshold criterion was 29.3%, and high-threshold criterion was 9.3%. The patients in our study were subjected to colposcopic examination after all the two screening procedures were performed that is Pap, VIA and the findings of colposcopy were correlated with them. Of the 400 women, majority of patients had Reid index ≤2 (87.25%) which was considered as normal. Abnormal colposcopic finding with Reid's index ≥3 was found in rest 51 (12.75%). When colposcopy was found to be normal (not suspicious of dysplasia) then abnormal Pap smear (≥LSIL) was found in 8 women, positive high-threshold VIA was found in 8 women, and low-threshold VIA was positive in 77 women. These values give an idea of false positive rates of the respective tests. Thus, low-threshold VIA had the highest false positive rate while Pap and high-threshold VIA had the lowest rate. Out of the 51 patients with suspicious colposcopy, Pap was positive (≥ASCUS) in 17 patients, high-threshold VIA in 29 patients, and low-threshold in 42 patients. There were 33 (9.24%) of normal or inflammatory Pap which showed suspicious colposcopy but out of these only 5 (1.4%) proved to be CIN2 on biopsy while 22 suspicious colposcopies were VIA negative of which only two were CIN 2 on biopsy. When low threshold is considered only 9 suspicious colposcopies were VIA negative out of which none was significant. This signifies the fact that if no lesion is to be missed low threshold should be the criteria. The women with suspicious colposcopy were then subjected to biopsy of the suspicious area. The biopsy rate was 12.75% with CIN 2 and 3 reported in 2.75 % and invasive cancer in 0.75%.

The study of Pap smear in the present study revealed a low prevalence of normal or negative smear (11.75%). Majority of the smears had inflammation (77.5%) which in Luthra's study were reported to be 70.3%.[9] In our study, ASCUS was seen in 5.5% of smears and LSIL in 2%, the corresponding figures mentioned in Novak's is 3-5% for ASCUS and 1.6% for LSIL.[10] The other findings were ASC-H in 0.25%, AGUS in 0.5%, HSIL in 1.5%, and invasive cancer in 0.5%. Our findings were like that reported by Osmanabad district RCT.[11] While Cronjé et al. 2003[12] reported a higher prevalence of LSIL and above smears, Luthra et al.[9] found lower prevalence (dysplasias 1.4% and carcinoma 0.15%). In contrary Ghosh et al., 2013,[13] reported abnormal Pap smear in 3.7% cases only while Saleh et al. 2013,[14] in an Egyptian study, as 4%. The present study used two thresholds of VIA to determine whether the specificity of the test can be further increased without any loss of sensitivity. The results of VIA were said to be high-threshold positive if the areas observed were opaque well-defined acetowhite lesions near the SCJ or as low-threshold positive if the indeterminate lesions (faint ill-defined and scattered acetowhite areas) were also considered. With high-threshold criteria, the positivity rate was 9.25%. But when faint acetowhite areas were also considered (low-threshold criteria) positivity rate was 29.75%, and the test was negative in 70.25%. In IARC study in Kerala in 1998-2000 low-threshold test was positive in 24.2% but when high-threshold criterion is used it was positive in 6.1%.[6] The

Table 3: Comparison of Pap smear and VIA in relation to reference standard (biopsy)

Parameters	Pap smear (≥LSIL)	Pap smear (≥HSIL)	VIA+	VIA++
Sensitivity (95% CI)	50.0 (23.0-76.9)	42.8 (17.6-71.2)	100 (76.8-100)	85.7 (57.2-98.2)
Specificity (95% CI)	97.6 (95.6-98.9)	99.4 (98.1-99.4)	72.8 (68.1-77.2)	93.5 (90.6-95.7)
PPV (95% CI)	43.7 (25.3-64.1)	75 (39.8-93.3)	11.7 (10.1-13.6)	32.4 (23.7-42.6)
NPV (95% CI)	98.1 (96.9-98.9)	97.9 (96.8-98.60)	100	99.4 (98.0-99.8)
Accuracy (%)	96	97.5	73.2	93.2

HSIL: High-grade squamous intraepithelial lesion, LSIL: Low-grade squamous intraepithelial lesion, VIA: Visual inspection with acetic acid, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

Table 4: Correlation of cytology with visual screening tests

Pap	VIA++ve	VIA+ve	Total
Normal	1	7	48
Inflammation	23	88	310
ASCUS	4	9	22
ASC-H	0	0	1
AGUS	1	1	2
LSIL	1	4	8
HSIL	4	6	6
Squamous cell carcinoma	1	1	1
Adenocarcinoma	1	1	1
Epithelioid granuloma	1	1	1
Total	37	119	400

++VIA: Positive with high-threshold criteria, +VIA: Positive with low threshold criteria, HSIL: High-grade squamous intraepithelial lesion, LSIL: Low-grade squamous intraepithelial lesion, ASCUS: Atypical squamous cells of undetermined significance, VIA: Visual inspection with acetic acid, AGUS: Atypical glandular cells of undetermined significance, ASC: Atypical squamous cells

positivity rates ranged from 3.1% to 38.7% in other reported studies.[15-18] One of the causes of such variation is different criteria considered in different studies due to lack of standard classification. The biopsy rate in present study was 12.75% while in the multicentric IARC study in India biopsy rate varied from 8.9% to 37.2%.[6] According to the study, the overall prevalence of cervical cancer and precursor lesions obtained was 3.5 %. The prevalence of CIN 2 and 3 was 2.75 %, and invasive cancer was 0.75% while in the Mumbai study by IARC (2005).[19] The prevalence of HSIL was 1.4% and invasive cancer was 0.7%. The estimated prevalence by Cronjé et al. of CIN 2 was 4.6%, and CIN3 was 2.8 % while invasive lesion was found in 0.8%.[12] Our study has taken three thresholds for consideration of Pap smear as positive. First taking ASCUS and above as positive, second, LSIL and above as positive and third HSIL and above as positive. There was 22 ASCUS on Pap of which only 6 had suspicious colposcopy and had cervical biopsy. On biopsy, only two were found to be CIN 2. When ACSUS is taken as threshold then the sensitivity of Pap in our study is 57.14%, specificity 92.22% NPV 98.34 % and PPV of 21.05%. The respective results of study in Kerala in 2003 are 81.9%, 87.8%, 99.3%, and 19.1%.[6] The results are similar except that Pap sensitivity is low in our study but that can be due to sampling error, preparation error or interpretation error in the multi-step process of evaluation of Pap. When LSIL and above smears were considered as threshold, then the sensitivity specificity were 50% and 97.66%, respectively, while NPV and PPV were 98.1% and 43.75%, respectively, in our study. The sensitivity of the Pap tests ranged between 29.5% and 62% and the specificity from 92.3% to 95% in various tests which took LSIL as threshold. The smear reporting HSIL in our study was 6 out of that 5 had suspicious colposcopy. These were then subjected to biopsy. 2 were found to be having CIN 2, rest one each had CIN3 and invasive squamous cell carcinoma. When HSIL and above was taken as threshold, then our study reported sensitivity of 42.85%, specificity 99.48%, NPV of 98% and PPV of 75% which were like the reporting of Nanda meta-analysis in 2000 (sensitivity of 53% and specificity of 96%).[20] The results of our study, as well as other studies, confirm the fact that cytology is a test with low sensitivity but very high specificity. Pap smear had the greatest sensitivity when ASCUS and above lesions were considered as positive, but the specificity was at its peak when HSIL and above lesions were taken as significant. The inherent limitations of the test that affects its sensitivity adversely are errors related to (i) sampling error -improper method of smear taking as well as spreading. The slide may be dried, thick, or clumping of cells can occur, (ii) failure to fix the slide immediately may also hamper the quality of slide, (iii) failure of cytotechnician to detect the abnormal cells, (iv) lack of exfoliation of abnormal cells may also account for the low sensitivity of the Pap test. In cases where sensitivity is required as in cases where only single visit of the patient is possible ASCUS as a threshold should be preferred whereas if multiple visits are there HSIL should be taken as a threshold as here true positive is required more than detecting false positives. Criteria should be uniform throughout the country to avoid confusion. VIA was evaluated according to the low- and high-threshold criteria as mentioned. The sensitivity of VIA with low-threshold criteria is 100% and specificity 72.7% in our study while the same in Kerala study it was 88.6% and 78.0%.[6] The specificities were similar but the sensitivity is quite high in our study. When high-threshold criteria were applied the sensitivity and specificity were 85.7% and 95%, respectively, which were higher than obtained from the Kerala study (sensitivity 82.6% and specificity 86.5%).[6] The comparison highlights the fact that the specificity of the high-threshold VIA (95%) is very high unlike other studies except for Sankaranarayanan who's in study specificity is 92%.[21] The other studies where clinician or nurse was involved, for example, EL-Shalakany et al., Slawson et al., and Megevand also reported a high specificity ranging from 84% to 98%.[18,22,23] Rest all have range varying from 54% to 84 %. While in Belinson et al. study where test providers were gynecologist still the results were not high.[10]

The present study evaluated both low- and high-threshold criteria of screening. If gynecologist do the VIA, referral for Pap would be less. If paramedics could be involved, then study could have drawn conclusion in that scenario.

CONCLUSION

Considering the study results, we conclude that VIA has better sensitivity than the conventional cytology in detecting premalignant lesions of the cervix. VIA with low-threshold criteria had high sensitivity (100%) although specificity (72.7%) was low this can be rectified by using high-threshold criteria for positivity which increases specificity up to 95% which is comparable to that of cytology (97.66%). Thus, VIA

with high-threshold criterion can be used by clinicians in tertiary-care centers where the patient can be directly subjected to further investigations and treatment at the earliest thus reducing loss to follow-up. The characteristics and accuracy of VIA encourage its use in not only rural settings but also well-established health care centers due to the high specificity shown in those settings. It is recommended that VIA should be routinely used as a screening test in all sexually active patients presenting to any of the health-care facilities. Accordingly, they can be further investigated, referred, or treated at the same visit whichever is cost-effective in that setting. A change in basic assumptions in global belief to move from the accepted wisdom that cervical cytology is the standard for cervical cancer screening to a new understanding that the visual screening methods also hold a significant potential is required. Visual screening tests are a new hope for bringing cervical cancer under control. How successful it is, remains to be seen.

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