Research Article

Visual Inspection with Acetic Acid -An Acceptable Option in Screening of Cervical Cancer

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Abstract

Objectives: To evaluate the accuracy of Visual Inspection with Acetic Acid (VIA) and Papanicolaou (Pap) smear as screening tests for cervical carcinoma and compare it with cervical biopsy as a gold standard.

Methods: This was a cross-sectional study conducted at Gynae Unit 3 Services Institute of Medical Sciences from Jan 2016 to December 2016. All the married patients between 18 to 64 years of age were included in the study. Every patient underwent VIA, Pap smear and colposcopic directed biopsy from acetowhite area as well as from 2:00 clock and 5:00 clock position. We determined the sensitivity, specificity, positive and negative predictive values of VIA, Pap smear and both tests and compared them with histopathology of biopsy specimen.

Results: 476 women were screened in the study. Out of these, 110 (23.10%) patients were VIA positive and 40 (8.40%) patients were positive with Pap smear. Thirty seven (7.77%) patients were positive on both VIA and Pap smear. A total of 43 (9.03%) patients had cervical pre-malignancy on biopsy. The sensitivity of VIA and pap was 97.67%, 94.87% while specificity was 84.29% and 99.31%respectively (p=0.001). The PPV of VIA and pap was 38.18% and 92.5 %(p=0.00) while NPV was 99.7% and 99.5% respectively. The sensitivity and specificity of both tests combined was 94.59% and 99.54% while the PPV and NPV was 94.59% and 99.54% respectively. Diagnostic accuracy of VIA was 85.5%

Conclusion: VIA has high sensitivity and NPV which makes it an e ective screening test for cervical carcinoma in developing countries like Pakistan. Pap smear can be combined to VIA positive cases to improve its specificity.

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Introduction

Cancer cervix is the fourth most common female cancer in developed countries and is second commonest cancer and a major cause of death from cancer in females in under-privileged countries. 525,000 new cases of cervical cancer are reported each year and most of these i.e. around 85% occur in developing countries.[1] Cervical cancer has a long pre-invasive state and if managed in pre-invasive stage, it is preventable. The incidence of cervical carcinoma has reduced by 50% in last 40 years in developed countries due to a well-established screening program. Screening by cervical cytology has markedly decreased morbidity and mortality due to CA cervix in developed world.[2] In contrast these

programs have not been well executed in developing countries as they do not have enough resources for implementation of cytology based prevention methodology, which necessitates well organized laboratories to collect material and specialized personal to render the diagnosis.[3] Moreover, it is expensive and patients need to make a second visit to collect report which often leads to loss of follow up.

There is need of a simple and inexpensive test which is convenient for the patient as well. Visual Inspection of cervix with Acetic Acid (VIA) which involves ability of trained health care personal to detect aceto-white area in the transformation zone of cervix fulfills these criteria. It is simple, easy and rapid to perform and can serve as a promising alternative to Pap smear in the developing countries.[4] Advantages of VIA include its low cost, immediate results, single setup, no laboratory processing or follow up visit required. WHO issued guideline in 2013 suggesting VIA as primary screening test for a wide range of settings with see and treat approach at the same visit in VIA positive patients as majority of patients are lost to follow up otherwise.[5] In Pakistan the screening program is poorly established because of multiple social and financial issues. There is only 1.9% coverage with cervical screening in spite of a high incidence of cervical cancer, reported to be 3.6% of all cancers.[6] Most of patients do not turn up with cytology report with the result that pick up rate of pre-cancerous stage is very low and majority of women present in advanced stage. In the prevailing situation, VIA can be a one step, low cost alternative method of screening. However, in Pakistan VIA is still not widely used as primary screening tool.

The rationale of our study was to evaluate the utility of VIA as primary screening tool in our setup. The study was designed to evaluate the sensitivity, specificity, predictive values and accuracy of VIA, Pap smear and combination against biopsy results as a gold standard.

Methods

After getting approval from institutional review board Services Institute of medical Sciences, this cross sectional study was conducted in Gynecology department, Services Hospital Lahore from January 2016 to December 2016. All married and sexually active women between 18 – 64 years presenting to Gynae OPD with any complaint were recruited in the study. Unmarried patients, those with bleeding PV or active infection at the time of examination, with frank invasive cervical cancer, bleeding disorder, previous abnormal cytology and pregnancy were excluded from the study. Detailed history regarding age, parity, vaginal discharge, age of marriage, irregular menses and post coital bleeding was taken. The procedure was explained and written in formed consent was obtained from all the enrolled patients. The procedure was performed by trained residents in Gynae OPD. A lubricated speculum was passed in vagina in lithotomy position and cervix was visualized under a light source. Any gross abnormality or discharge was noted. Excess mucus and discharge were removed gently with swab. The squamo-columnar junction (SCJ) was visualized in its entire extent; Pap smear was taken with Ayer's spatula, spread on a glass slide, fixed and labeled. A swab was soaked in 5% acetic acid and applied to the cervix for one minute. Acetic acid makes pre-cancerous areas turn white. The acetowhite area adjacent to SCJ was termed as VIA positive. To compare accuracy of two screening tests with gold standard, colposcopic directed biopsy was then taken from the VIA positive areas as well as from 2 'o' clock and 5 'o' clock positions in all the patients. Pap smear samples and the biopsy samples were submitted to the pathology lab of SIMS by the concerned resident and Lab number was recorded in a register at Gynae OPD clinic for retrieval of reports. Pap smear was taken positive if it showed low or high grade intraepithelial lesions or atypical squamous cells of undetermined significance (ASCUS). Biopsy report of CINI, II and III was taken as positive.

The results of VIA, Pap smear and biopsy were recorded on a structured data collection tool, purposely designed for the study. After desk editing, the data was entered in SPSS computer software Version 20. Validation analysis was done to estimate the sensitivity, specificity, predictive values and accuracy of VIA, Pap smear and combination against biopsy results. The estimated validation parameters were mutually compared by using standard of errors of di erence between two proportions. P value of 0.05 was used as significance level for the di erence between VIA, Pap smear and combination.

Results

During the study, 539 women were recruited and of these, 476 were analyzed. 63 (11.67%) were excluded as the reports of either Pap smear or biopsy were not

available. The mean age was 38.36 +_ 8.629 years and majority 392 (82.35%) were multipara. 68 (14.3%) patients were below 18 years of age at marriage while 82.4% were married at 18-22 years. 42% had high school education and 94.5% were housewives(Table 1)

Table 1: *Patient Characteristics*

Variables	Frequency	VIA Positive	Pap Positive	Biopsy Positive
Age (Years)				
<20	20 (4.2%)	1 (0.9%)	0 (0%)	0 (0%)
20-29	100 (21%)	15 (13.6%)	3 (7.5%)	0 (0%)
30-39	144 (30.3%)	46 (41.8%)	15 (37.5%)	13 (30.2%)
40-49	160 (33.6%)	39 (35.4%)	20 (50%)	25 (58.1%)
50-59	48 (10.1%)	8 (7.2%)	2 (5%)	5 (11.6%)
>60	4 (0.8%)	1 (0.9%)	0 (0%)	0 (0%)
Total	476 (100%)	110 (100%)	40 (100%)	43 (100%)
Age at the Time of Marriage				
below 18	68 (14.3%)	9 (8.18%)	2 (5%)	1 (2.3%)
18-22	276 (58%)	67 (60.9%)	27 (67.5%)	26 (60.4%)
23-28	116 (24.4%)	30 (27.2%)	10 (25%)	15 (34.8%)
above 28	16 (3.4%)	4 (3.6%)	1 (2.5%)	1 (2.3%)
Parity				
P1-P2	84 (17.6%)	26 (23.6%)	3 (7.5%)	4 (9.3%)
P3- P5	336 (70.6%)	64 (58.1%)	23 (57.5%)	20 (46.5%)
P6 and above	56 (11.8%)	20 (18.1%)	14 (35%)	19 (44.1%)
Total	476 (100%)	110 (100%)	40 (100%)	43 (100%)
Contraceptive Methods				
Natural	278 (58.4%)	50 (45.4%)	16 (40%)	21 (48.8%)
Barrier	54 (11.3%)	19 (17.2%)	3 (7.5%)	5 (11.6%)
IUCD	72 (15.1%)	27 (24.5%)	12 (30%)	10 (23.2%)
BTL	66 (13.8%)	14 (12.72%)	8 (20%)	7 (16.2%)
Hormonal	6 (1.2%)	0 (0%)	1 (2.5%)	0 (0%)
Total	476 (100%)	110 (100%)	40 (100%)	43 (100%)
Occupation				
Housewives	450 (94.5%)	106 (96.3%)	34 (85%)	40 (93.0%)
Teachers/medical profession	16 (3.37%)	2 (1.8%)	4 (10%)	2 (4.6%)
Others	10 (2.13%)	2 (1.8%)	2 (5%)	1 (2.3%)
Total	476 (100%)	110 (100%)	40 (100%)	43 (100%)
Educational Status				
Uneducated	100 (21%)	62 (56.3%)	24 (60%)	26 (60.4%)
Elementary	172 (36.1%)	30 (27.2%)	10 (25%)	12 (27.9%)
Matric	200 (42%)	14 (12.7%)	6 (15%)	5 (11.7%)
Graduation	4 (0.8%)	4 (3.6%)	0 (0%)	0 (0%)
Total	476 (100%)	110 (100%)	40 (100%)	43(100%)

Out of 476 patients, 110 (23.1%) patients were VIA positive while 40 (8.40%) patients had positive Pap smear. A total of 43 (9.03%) patients had cervical pre-malignancy on biopsy. Out of these, 23 had CINI, 15 had CINII and 5 had CINIII. The sensitivity of VIA and pap was 97.67%, 94.87% while specificity was 84.29% and 99.31% respectively. The PPV of VIA and pap was 38.18% and 92.5 %while NPV was 99.7% and 99.5% respectively. The sensitivity and specificity of both tests combined was 94.59% and 99.54% while the PPV and NPV was 94.59% and 99.54% respectively. Diagnostic accuracy of VIA was 85.5%. Diagnostic accuracy of VIA and Pap is 85.5% and 98.9% (Table 2, 3).

Table 2: *Diagnostic Accuracy of VIA, PAP and Combination with Biopsy as Gold Standard*

VIA	Biopsy Positive	Biopsy Negative	Total
Positive	**42**	68	110
Sensitivity	**97.6%**	15.8%	23.1%
PPV	**38.2 %**	61.8	100.0%
Negative	1	**365**	366
Specificity	2.4%	**84.2%**	76.9%
NPV	0.3%	**99.7%**	
Total	43	433	476
	100.0%	100.0%	100.0%
Pap Smear			
Abnormal	**37**	3	40
Sensitivity	**94.8%**	0.7%	8.4%
PPV	**92.5%**	7.5%	100.0%
Normal PAP	2	**434**	436
Specificity	5.2%	**99.3%**	91.6%
NPV	0.5%	**99.5%**	100.0%
Total	39	437	476
	100.0%	100.0%	100.0%
Combination of VIA + Pap			
Positive	**35**	2	37
Sensitivity	**94.5%**	0.5%	1.8%
PPV	**94.5%**	5.5%	100.0%
Negative	2	**437**	439
Specificity	5.5%	**99.5%**	92.2%
NPV	5.5%	**99.5%**	100.0%
Total	37 (100.0%)	439 (100.0%)	476 (100.0%)

Table 3: *Comparison of Screening Indices of VIA and Pap Smear with Biopsy as Gold Standard*

Diagnostic Accuracy	VIA	Pap Smear
Sensitivity	97.67%	94.87%
Specificity	84.29%	99.31%
PPV	38.2 %	92.5 %
NPV	99.7%	99.5%
False Positive Rate (FPR)	15.8%	0.7%
False Negative Rate (FNR)	2.4%	5.2%
Diagnostic Accuracy	85.5%	98.9%
True Prevalence	9.03%	8.2%
Presumed prevalence	23.1%	8.4%
Positive Likelihood ratio	6.2	135.4
Negative Likelihood ratio	0.029	0.05

Discussion

Despite evidence that incidence of cervical cancer has reduced markedly in certain regions of the world and survival in women with this cancer has improved, more than 2 million women still continue to su er from this cancer worldwide. In developing countries many women die from cervical cancer each year as e ective screening programs don't exist. Cervical cancer is a potentially preventable carcinoma and if detected early and properly treated with simple procedures has almost 100% cure rate. In this study, 476 patients were screened with VIA and Pap smear. All the patients were subjected to colposcopic directed Biopsy. This enabled us to calculate sensitivity, specificity, PPV and NPV reliably, whereas in most of the studies, only screened positive patients were subjected to Biopsy.[7,8]

In our study the mean age of patients was 38.36 years. The peak age reported by various studies is 32-39 years.[7] This age is important to target for cervical cancer screening as conservative treatments can be o ered at this stage and overt malignancy can be avoided. Screening programs in developed countries recommend screening to start at 25 years. ASCO recent guidelines have included screening for basic settings and recommend that in developing world women to be screened one to three times from 30-49 years.[9] Majority (88.2%) of our patients were multipara. Cervical cancer is more common in multiparous women.[6,7] Early marriage is proposed a strong risk factor for cervical malignancy as it is associated with increased number of sexual exposures.[8] In our study, only 14.8% of women had early marriage and only one of them had CIN. Altered sexual behavior with exposure to Sexually transmitted infections in relation to number of partners is more important a risk factor which is unfortunately not reported in our setup as majority of women are reluctant to give information in this regard. Separate STI clinics are a taboo and women continue to su er in silence.

VIA positive rate in screened women in our study was 23.10%. Studies conducted so far report a wide range of VIA positive rate. This wide variation in rate is due to di erent criteria used in di erent studies because of lack of standardization of positive results and as VIA is subjective, interpretation of observer may be di erent. Poli UR reports 10% VIA positive rate, Muhammad et al reported 6% and Saleh et al reported VIA positive in 28.7% of women.[10,11] The reason for a high VIA positive rate (23.10%) in our study could be two fold. First, the presence of infection takes up the stain and area appears aceto white. Secondly, some faint aceto white areas might have been considered positive. High false positive results of VIA are also reported from IARC study from India and Africa.[12] VIA is an observant dependent test relying on the expertise and level of health care provider. This emphasizes the importance of training of persons involved for optimum interpretation and thus reduce the number of false positive cases.

Di erent studies have reported a wide range of sensitivity and specificity for VIA. A study in Bangladesh on 650 women has reported high sensitivity and low specificity of 88.9% and 52%which is similar to our study where VIA was found to be highly sensitive (97.67%) while specificity was relatively low (84.2).[8] In contrast Mahmood G has reported low sensitivity(78%) but a very high specificity (99.3%).[12] Di erent studies have used di erent criteria for ruling out VIA negative cases as majority have taken biopsy of positive cases only and healthy look of the cervix is assumed to be a true negative test. In our study PPV of VIA was relatively low(38.18%) which is probably attributed to a large number of false positive cases due to infections and inclusion of very faint aceto white areas. NPV of VIA was 99.72% in our study and is comparable to other studies which show NPV of 92-99.5%.[8,11,12] Due to high NPV of VIA, women can be reassured that they are unlikely to have cervical neoplasia in case they are VIA negative.

The sensitivity of Pap smear reported in our study was 94.87% and specificity was 99.31%. Studies have reported sensitivity ranging from 33.3% to 83% and specificity ranging from 83% to 99.4%.[8,12,13] In our study, VIA had high sensitivity but low specificity than Pap smear in detection of cervical cancer. The PPV of VIA was significantly low (38.18%) as compared to Pap smear (92.5%) $P<0.05$, whereas the NPV of VIA and Pap were comparable ($P<0.01$).The specificity and predictive accuracy of VIA was significantly less than Papp smear and combination of two tests. Ibrahim A and Mahmood G have also shown combined test to be superior to both tests alone.[12] Owing to its high sensitivity, high NPV and diagnostic accuracy of 85%, VIA can replace Pap

smear for universal cervical cancer screening in low resource countries like Pakistan. High-false positive rate in VIA based screening program is a major concern which can be reduced by performing Pap smear of VIA positive cases to increase specificity in places where colposcopy is not available.

In our study, all the patients were subjected to cervical biopsy and the results were authenticated. Moreover, in conclusion VIA came out to be a simple, cost e ective and reliable mode of investigation in cervical cancer screening which is easy to apply in OPD setup.

It was a hospital based study and we could not screen general population so it was not a true representation of disease in general population.

Conclusion

VIA is a simple, one step, cost e ective test for cervical screening which can be implemented as part of cervical cancer screening program in developing countries like Pakistan. Although VIA has low specificity as compared to Pap smear, its advantages outweigh its limitation of having high false positive rate. High NPV reassures a woman against cancer. Specificity can be improved by better training of health care providers and combining Pap smear in VIA positive cases.

Ethical Approval: Given

Conflict of Interest: None

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