International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Diagnostic Efficacy of Visual Inspection with Acetic Acid (VIA) in Cervical Cancer Screening in Women Aged 20-60 Years

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Running Title: *VIA in Cervical Cancer Screening*

Compliance with ethical standards

Conflict of Interest- There is no conflict of interests between the authors.

Informed Consent- Informed consent was obtained from all individual participants included in the study.

Abstract: ***Aim: To assess the efficacy of VIA as cervical cancer screening in women aged 20-60 years by comparing it with cytology, colposcopy and using cervical biopsy histopathology as gold standard. Methods: The study population consisted of 500 women. Freshly prepared 5% acetic acid was applied to the cervix and inspected after one minute. Women were subjected to cytology, colposcopy and histopathology as well. Using histopathology as the reference standard, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of VIA, cytology and colposcopy was calculated. Statistical significance was calculated by P value ≤0.05. Results: VIA had higher sensitivity & negative predictive value of 78.04% & 96.32% respectively, than LBC and colposcopy. LBC & colposcopy had higher specificity and positive predictive value than that of VIA. VIA showed the highest percentage of false positives (54.3%) while the lowest percentage of false negatives (21.9%). Conclusions: VIA can be used as an initial screening test for cervical cancer in low resource countries like India. Cytology had high sensitivity and comparatively higher specificity and therefore can be used for screening in conditions when there are no financial constraints.***

Keywords: Cervical cancer screening, visual inspection with acetic acid, cytology, colposcopy

1. Introduction

Cancer cervix is a significant global public health problem, especially in developing countries where it is the most common cancer in women. Worldwide, an estimated 500,000 new cases of cervical cancer are identified every year leading to annual mortality of 270,000[1]. In India, 1,32,000 new cases of cancer cervix are detected per year & 74,000 deaths take place due to this disease each year[1].

The risk factors for cervical cancer include early age at first intercourse (less than 16 years), multiple sexual partners, cigarette smoking, high parity, low socioeconomic status, race, genital infections like chlamydia. Sexually transmitted HPV has been implicated as a causative factor in more than 97% of all cancers of the cervix[2] hence, all sexually active women constitute the risk group. The carcinogenic HPV strains are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. HPV infection usually resolves in 90% of cases over a period of 18-24 months[3], persistence of the infection progresses to CIN and frank invasive carcinomas later on as long as over 15-20 years Thus, the disease has a long latent period that provides us opportunity to screen and catch in its premalignant phase only.

According to GOI-WHO 1992/2006, organized cervical cancer screening programmes are not feasible in India, due to huge population, inadequate infrastructure, lack of trained human resource, logistic difficulties, relatively high cost, & suboptimal follow-up/treatment of screen-positive women & so suggested an alternative scientifically valid simple screening strategy in resource poor areas, i.e, VIA (Visual Inspection by Acetic acid). This is a simple, cheap and highly sensitive screening modality that is much simpler and significantly lesser costly than Pap smear.

2. Materials and Methods

Type of Study- Observational

Place of study- Department of Obstetrics & Gynecology, MotiLal Nehru Medical College, Prayagraj in over a period of one year.

Sampling method- Incidental sampling
Inclusion criteria- All sexually active women aged 20 – 60 years attending OPD after obtaining informed consent.

Exclusion criteria- Women < 20 years old, women > 60 years old, non-sexually active women, pregnant women,

patients with already diagnosed vaginal, vulval and cervical neoplasia, patients not giving consent.

Procedure-

- VIA and cytology was done in all 500 cases (LBC in 68 cases and conventional PAP smear in rest 432 cases). Cytology was reported as per Bethesda classification and was interpreted as positive when either of ASCUS/ASC-H/ LSIL/ HSIL were there.
- Colposcopy was done in 374 cases, which included all VIA positive cases, abnormal cytology cases as well as some normal patients who were VIA & cytology negative, so as to include them as control. Swede scoring system was used for interpreting colposcopic findings.
- Cervical biopsy was done in 315 cases including all VIA positive patients, cytology positive patients & abnormal colposcopic findings as well as again in some normal patients who were VIA/cytology/colposcopy negative, so as to take them as control.
- Sensitivity, specificity, positive predictive value and negative predictive value was calculated for VIA, cytology and colposcopy using histopathology as the reference standard, and the diagnostic efficacy of VIA was assessed.

Statistical analysis

Statistical significance was determined by Chi square test. P value ≤ 0.05 was taken as critical level of significance.

3. Results

Table 1-*Age distribution* – Maximum; 42% belonged to 31-40 years age group, followed by 27.2% in age group of 20-30 years and least 12.8% belonged to 51-60 years age group. The overall mean age of the group was 36.64 + 9.34 years.

Parity - *Majority* were of parity >3, i.e. 38.4% followed by parity 3, i.e. 32.2%.

Age of onset of sexual activity – Maximum, 83.2%, had the age of onset of sexual activity between the age group of 18-25.

Presenting Complaint- Majority, 52.6% had complained of discharge per vaginum followed by abnormal uterine bleeding (20.2%) & post-coital bleeding (2.8%). While 24.4% cases were asymptomatic.

Table 2: Via & Age Distribution in Relation to Via (N=500)

VIA positivity was 14%; with maximum in age group 31-40 years and minimum in 51-60 years with statistically significant (p value=0.024) age distribution.

Table 3- Liquid Based Cytology/ Conventional Pap Smear Reports (N=500)

Normal smear were found in 33.2% women; ASCUS/ASC-H was found in 4.0%; while 5.6% had LSIL; HSIL was present in 1.0%. The results were statistically significant (p value<0.0001).

Colposcopic Findings (N=374)

CIN I was present in 3.2% women; 1.3% had CIN II; while only 0.2% had CIN III.

The results were extremely statistically significant (p value<0.0001).

Cervical Biopsy Histopathology Reports (N=315)

CIN I was found in 9.5% cases; 1.6% had CIN II; while 0.9% had CIN III & 0.9% cases had microinvasive cancer.

Table 4– Comparison Between Via (N=500) and Cytology Reports (N=500), Colposcopy (N=374), Cervical Biopsy Histopathology (N=315)

On comparing VIA and cytology, 65.7% were VIA positive, 1.6% were VIA negative.
On comparing VIA & colposcopy findings, 20.0% were VIA positive, 1.2% were VIA negative.
On comparing VIA & histopathology, 45.7% were VIA positive, 3.7% were VIA negative.

Table 5- Sensitivity, Specificity, Positive Predictive Value & Negative Predictive Value Of Via, Cytology & Colposcopy. In this study, the true positives were defined as CIN I/II/III & microinvasive cancer in histopathology and parameters were calculated taking histopathology as standard.

The calculated sensitivity of VIA was 78.04%; specificity was 86.15%; PPV was 45.71%; NPV was 96.32%.

The calculated sensitivity of cytology was 48.7%; specificity was 95.2%; PPV was 60.6% and NPV was 92.5%. The calculated sensitivity of colposcopy was 31.7%; specificity was 98.1%; PPV was 72.2% and NPV was 90.5%.

4. Discussion

We had maximum patients in the age group 20-40 years, with parity ≥ 3 and start of sexual activity between 18-25. Since these are known risk factors for cancer cervix, our study population consisted of maximally representative women.

VIA positivity rate of 14% is comparable to the results of **Usha Rani et al; 2015**[7] who did study in Andhra Pradesh and found positivity rate of 10.75%, and to **S. Consul et al; 2012**[8] who conducted study in Delhi that is comparable to our demographic region and found positivity rate of 13.7%.

Statistically significant (p=0.024) VIA positivity in age group 31-40 years as has been found in our study has also been noticed by **L. Satyanarayana et al; 2014**[9] in North India. This finding explains the maximum occurrence of female cancer cervix in age group 60-65 years as well as this justifies the statement issued by WHO – "that every woman even in low resource settings should have screening atleast once in lifetime that too beyond 30 years" so as to catch the maximum cases[6]. Least VIA positivity in women aged > 51 years is basically due to chances of receded transformation zone after menopause.

Cytology positivity rate of 10.6% in present study is comparable to 10.3% Pap smear positive rate in the study done by **Sinha P et al[10] in 2018** in Lucknow. Colposcopic positivity rate (CIN I/II/III) of 4.7% was comparable to 2.4% colposcopic positive (CIN 2-3) rate in the study done by **S.A Pimple et al, 2010[19];** and biopsy positivity rate was 13.9 %.

Out of all above described positivities, the maximum were LSIL in PAP smear, CIN I in colposcopy and cervical biopsy. Maximum positivity of these initial premalignant lesions reemphasize the importance of cervical screening and better understanding of the clinician for further management. Lack of proper knowledge and attitude of panic may result in overtreatment of these women who are usually in reproductive age group and are in need of anatomically and physiologically normal uterus and cervix, as most of these lesions (upto 80-85%) get spontaneously healed by the time and just a careful followup is required[2,3].

While assessing the efficacy of VIA positivity by comparing them with cytology, colposcopic and cervical histopathological positivity showed that VIA positivity was statistically significantly ($p < 0.0001$) correlated with all three. Since histopathology is the gold standard, the positive association between VIA positivity and histopathology positivity can be taken as the most predictive parameter for assessing the sensitivity of VIA. CIN findings were significantly higher in patients with VIA positivity.

At the same time the study also assessed the false negativity of VIA by observing PAP smear/ colposcopic/ histopathology positivity. The false negativity as per PAP smear and Colposcopy was 1.6% and 1.2% but when histopathology was taken as the parameter, the false negativity rose up to 3.7%. Almost similar observations were observed by **S. Anitha Rani et al[4] (2016)** where 3.7% cases which were negative on VIA/VILI were reported as LSIL in cytology.

Sensitivity, specificity, positive predictive value & negative predictive value of VIA of 78.4%, 86.15%, 45.71% and 96.32% respectively were comparable to studies done by **Divya Hedge et al[13], Singh KN et al[15], Sankaranarayana et al[18] and Rana T et al[17].**

Though histopathology is the gold standard in detecting the abnormalities, it has its own limitations to be adopted as screening tool for cancer cervix. Colposcopy also cannot be made widely available and even if we succeed in making it available, the interpretation requires high quality knowledge. VIA comes out to be the simplest method of screening and since the study shows its high sensitivity, specificity, PPV and NPV, it can be adopted as a screening tool.

Though seems little irrational, practically some of false negativities of VIA may be ignored if we can succeed in its widespread use even at the most peripheral level as screening tool to detect premalignant conditions using its high sensitivity and specificity.

5. Conclusion

The sensitivity of VIA was more than both cytology and colposcopy. However the specificity was comparatively lower. Positive predictive value was more for colposcopy, Negative predictive value was higher for VIA followed by cytology & colposcopy. The percentage of false positives was highest with VIA, but the percentage of false negatives was lowest with VIA.

For any screening modality, the requirement is to have highest sensitivity and VIA has shown to be having 78.04% sensitivity with good enough specificity too (86.15%). So, VIA fulfills all the criteria to be implemented as a screening tool for cancer cervix on the scientific grounds also.

The results and analysis show that by opting VIA as a screening procedure the chances of missing out abnormal cases are acceptably low. Utilizing its high sensitivity in picking up the abnormal cervix and treating them at the same time with ablative measures, as indicated by WHO in the guideline[6] issued in year 2013 recommending "See and Treat", so as to avoid the missing out of the screen positive patients, will definitely help in reducing the incidences of cancer cervix in developing countries too.

Table 1: Age Distribution, Parity, Age of Onset Of Sexual Activity & Chief Complain (N = 500)

Age Group (Years)	No.	%	Parity	No.	%	Age of Onset of Sexual Activity	No.	%	Chief Complain (N=500)	NO.	%
20-30	136	27.2	<1	34	6.8	<18	56	11.2	Asymptomatic	122	24.4
31-40	210	42.0	2	113	22.6	18-25	416	83.2	Discharge per vaginum	263	52.6
41-50	90	18.0	3	161	32.2	>25	28	5.6	Abnormal uterine bleeding	101	20.2
51-60	64	12.8	>3	192	38.4	-	-	-	Post coital bleeding	14	2.8
Total	500	100	Total	500	100	Total	500	100	Total	500	100

Table 2: Via & Age Distribution in Relation to Via (N=500)

VIA (N=500)	Positive	%	Negative	%
	70	14.0	430	86.0
AGE	**Positive**	**%**	**Negative**	**%**
20-30 (x=136)	12	17.1	124	28.8
31-40 (x=210)	34	48.6	176	40.9
41-50 (x=90)	16	22.9	74	17.2
51-60 (x=64)	8	11.4	56	13.1
Total	70	100	430	100
p value – 0.024*				

Table 3: Liquid Based Cytology/ Conventional Pap Smear Reports (N=500), Colposcopic Findings (N=374) & Cervical Biopsy Histopathology Reports (N=315)

Cytology Reports (Lbc/Conventionalpap)	No.(%)	Colposcopic Findings	No.(%)	Cervical Biopsy (N=315)	NO.(%)
Normal No. (%)	166(33.2%)	Normal No. (%)	345(89.3%)	Normal No. (%)	112(35.6%)
Inflammatory No. (%)	281(56.2%)	Leukoplakia No. (%)	11(2.8%)	Cervicitis No. (%)	162(51.5%)
ASCUS/ASC-H NO. (%)	20(4.0%)	CIN I NO. (%)	12(3.2%)	CIN I NO. (%)	30(9.5%)
LSIL NO. (%)	28(5.6%)	CIN II NO. (%)	5(1.3%)	CIN II NO. (%)	5(1.6%)
HSILNO. (%)	5(1%)	CIN III NO. (%)	1(0.2%)	CIN III NO. (%)	3(0.9%)
Invasive Cancer No. (%)	0	-----	-----	Microinvasive Cancer NO. (%)	3(0.9%)
Total No. (%)	500(100%)	TOTAL NO. (%)	374 (100)	Total No. (%)	315(100%)
p value-0.0001*		**p value-0.004**		**p value-0.0001***	

Table 4: Comparison Between Via (N=500) and Cytology Reports (N=500), Colposcopy (N=374), Cervical Biopsy Histopathology (N=315)

Cytology Reports	VIA Positive (n=70) No. (%) / VIA Negative (n=430) No. (%)	Colposcopic Findings	VIA Positive (n=70) No. (%) / VIA Negative (n=304) No. (%)	Histopathological Diagnosis	VIA Positive (n=70) No. (%) / VIA Negative (n=245) No. (%)
Normal (n= 166)	0 / 166 (38.6%)	Normal (n=345)	56 (80.0%) / 289 (95.2%)	Normal (n=102)	0 / 102 (41.6%)
Inflammation (n= 281)	24 (34.3%) / 257 (59.8%)	Leukoplakia (n=11)	0 / 11 (3.6%)	Chronic cervicitis (n=272)	38 (54.3%) / 134 (54.7%)
ASCUS /ASC-H/LSIL/HSIL (n= 53)	46 (65.7%) / 7 (1.6%)	CIN I/CIN II/ CIN III (n=18)	14 (20.0%) / 4 (1.2%)	CIN I/ CIN II/ CIN III/ Microinvasive cancer (n=41)	32 (45.7%) / 9 (3.7%)
Total (n= 500)	70 (100.0) / 430 (100.0)	Total (n=374)	70 (100.0) / 304 (100.0)	Total (n=315)	70 (100.0) / 245 (100.0)
p value	0.0001*	p value	0.0001*	p value	0.0001*

Table 5: Sensitivity, Specificity, Positive Predictive Value & Negative Predictive Value of Via, Cytology & Colposcopy

%	SENSITIVITY	SPECIFICITY	PPV	NPV
Via	78.04 (95% CI; 65.3-90.7)	86.15 (95% CI; 82.0-90.2)	45.71 (95% CI; 34.0-57.3)	96.32 (95% CI; 93.9-98.6)
Cytology	48.7 (95% CI; 33.4-64.0)	95.2 (95% CI; 92.7-97.7)	60.6 (95% CI; 43.9-77.2)	92.5 (95% CI; 89.4-95.6)
Colposcopy	31.7 (95% CI; 17.4-45.9)	98.1 (95% CI; 96.5-99.7)	72.2 (95% CI; 51.5-92.9)	90.5 (95% CI; 87.2-93.8)

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