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Comparative Study of VIA and PAP Smear As a Screening Tool for Preinvasive and Early Invasive Cervical Cancer

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Abstract:

Introduction *- Cervical cancer is the 2nd common cancer among women worldwide. It is also the leading cause of cancer related mortality in women globally. Due to lack of effective screening program in developing countries, majority of cervical cancer deaths happen in low resource countries. Well organized screening program by cytology has substantially reduced burden of cervical cancer in developed countries, however in developing countries, pap smear based screening program is not feasible due to lack of infrastructure, trined personnel and labs, and funds. Thus alternate screening methods have been studied. Visual screening methods that are simple, cheap and give instant results have been widely studied. In this study we compared the test performance of VIA and PAP screening*

Material and methods *- This is a cross sectional study conducted at CCM medical college, kachandur, durg, between May 2016 to December 2016 over a period of 6 months in Gynae OPD using the existing infrastructure and manpower. All sexually active women between 21-65 yrs of age coming to gynae OPD with various complaints were screened with VIA /VILI and PAP smear in their first visit. Positive cases underwent biopsy and histopathological study done. The sensitivity, specificity, PPV and NPV of VIA and PAP for detection of CIN and early invasive ca cx was determined and compared.*

Results *- Sensitivity of VIA in our study is 97 % but specificity is 56 %. Positive predictive value of VIA thus is low ie 52.25%. But negative predictive value is very good, about 97 %. Hence VIA test is an ideal screening tool as it is unlikely to miss any lesion esp high grade lesion. But it may over diagnose hence lead to more no of patients referred or subjected to colposcopy and biopsy. For PAP test sensitivity is very low it is coming to 39.5% in our study. But specificity was close to 90 %. One more drawback of PAP is lost to follow up as reports are available after 4-5 days and many patients do not come for follow-up hence many positive e cases might be missed. Comparing both the tests VIA is more sensitive while PAP is more specific.*

Conclusion *- VIA can be used as a screening test for cervical cancer and CIN as it is easy, cheap, quick and simple. It does not require any additional infrastructure or cost to do the test. Hence can be easily implemented in low resource settings at grass root level.*

Keyword *- VIA, PAP, cervical cancer, CIN, Screening*

Aim

To compare sensitivity, specificity of VIA and Pap smear for screening of pre-invasive and early invasive cervical cancer.

Introduction

Cervical cancer is the 2nd common cancer among women worldwide. It is also the leading cause of cancer related mortality in women globally. Due to lack of effective screening program in developing countries, majority of cervical cancer deaths happen in low resource countries. 1/5th of global burden of cervical cancer is in India. Cervical cancer continues to be a major public health problem in India with an incidence of 134,420 cases and mortality of 72,825 cases in the year 2008.[1]

Well-organized screening by cytology has substantially reduced the incidence of morbidity and mortality from cervical cancer in developed countries.[2-4] However, in

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developing countries like India, universal screening has not been achieved. The main screening method (Pap smear) is available to a small percentage of population. Cytology based screening programmes are difficult to organize owing to limited infrastructure, trained personnel and funds.[5]

In Chhattisgarh state majority of polulation is in rural areas and tribal areas who do not have access to basic healthcare facilities. Majority of cervical cancer cases present in advanced stages due to lack of screening facilities. Most women detected with cervical cancer are in stage3 or 4 beyond the stage when curative treatment can be done. They have to travel long distances for their treatment. Many times they succumb to the disease as they have no means to travel frequently for their treatment.

With the current infrastructure and facilities available and lack of any organized screening program to implement cytology based screening is not possible due to lack of proper labs and trained cytopathogists who are available only in selected centres in cities. Also the need to come again for the report deters many women from getting the test done. Hence low cost visual screening methods for screening of preinvasive and invasive cervical cancer - VIA and VILI that gives instant results have been studied. This test is a simple, cheap and quick method of screening and can be taught to paramedics, nurses and community healthcare providers.

In this study we compared the sensitivity, specificity, PPV and NPV of VIA and PAP smear as a screening tool for CIN and early cervical cancer.

Material and Methods

This is a cross sectional study conducted at CCM medical college, kachandur, durg, between May 2016 to December 2016 over a period of 6 months in Gynae OPD using the existing infrastructure and manpower.

All sexually active women between 21-65 yrs of age coming to gynae OPD with various complaints were screened with VIA/VILI and PAP smear in their first visit. Positive cases underwent biopsy and histopathological study done. The sensitivity, specificity, PPV and NPV of VIA and PAP for detection of CIN and early invasive ca cx was determined and compared

Overall 1790 women were screened with VIA /VILI and PAP smear between may 2016 and dec 2016 all women in the first vist to gynae OPD were sent to cancer screening OPD and thorough history and evaluation done .speculum exam done and visual inspection under good light after application of 5% acetic acid done for all. Finding recorded after 1 min. All cases with acetowhite areas in transformation zone were considered VIA positive. After this Pap smear was taken with help of ayer's spatula, slide prepared and fixed and send for cytopathological analysis. finallly Lugol's iodine applied and negative areas recorded as VILI negative. This was used to enhance and reinforce the findings of VIA but not taken into account while calculating the sensitivity and specificity of VIA.

These patients were then sent to gynae OPD for routine evaluation as per their complaints patients with cervicitis and vaginitis were given antibiotic treatment .Followup visit after 7 days done .patients with either test positive were offered cervical biopsy.

Findings of VIA and PAP were correlated and compared with Biopsy and histopathology.

Sensitivity, specificity, positive predictive values and negative predictive values of both VIA and PAP calculated on basis of available data. p value and X2 test used for statistical analysis.

Observations and Results

The observations of the study are as presented here.

Total of 1790 patients were screened with VIA/VILI and PAP smear.

VIA was positive in 476 patients (26.6%) and PAP was positive in 73 patients (4.07%)

Age of patients screened ranged from 22 to 70 years with a mean age of 46 yrs. we screened all women coming to gynae OPD who are sexually active irrespective of their presenting complaint except those with active bleeding.

Table 1: Correlation of PAP screening results with VIA screen results

VIA result	Total pap +	PAP -ve	ASCUS	LSIL	HSIL
VIA +	57	419	7	12	38
VIA -	16	1298	11	5	0
	73	1717	18	17	38

57 patients were both PAP and VIA +ve; 419 patients were VIA +ve but PAP –ve; 16 patients were PAP +ve but VIA –ve, 1298 patients were both PAP and VIA -ve.

Out of total PAP positive cases 18 were ASCUS, 17 were LSIL and 38 were HSIL.

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Table 2: PAP results correlation with histopathology result

Biopsy	PAP +ve	PAP -ve	Total
Positive (CIN 1 and above)	47(64.3%) True positive	73 False negative	120
Negative Chronic cervicitis /normal)	26(35.6%) False positive	220 True negative	246
total	73	293	366

Out of 73 PAP +ve cases, 47(64.3%) were positive on biopsy (CIN 1 and above)-true positive

And 26(35.6%) were negative (chronic cervicitis or normal) on biopsy. (False positive)

Out of PAP negative cases 73 patients were positive on biopsy (false negative), so PAP smear actually missed these cases.

Table 3: VIA result correlation with histopathology results

Biopsy	VIA +ve	VIA -ve	Total
Positive((CIN 1 and above)	120 True positive	3 False negative	123
Negative (Chronic cervicitis /normal)	103 False positive	140 True negative	243
	223	143	366

Out of 476 VIA positive cases, biopsy was done in 223 cases, and biopsy was positive in 120 cases (true positive) and negative in 103 cases so in these cases VIA was falsely positive .Of the VIA negative cases, biopsy was also negative in 140 cases (true negative); and positive in only 3 cases (false negative) that too were CIN 1 cases. Thus VIA missed only 3 cases on CIN 1 no case of high grade CIN or Ca cx was missed by VIA

Table 4: Histopathological correlation of PAP positive cases PAP positive - total 73

PAP → biopsy		ASCUS		LSIL		HSIL	
		VIA +	VIA -	VIA +	VIA-	VIA +	VIA-
Negative	Chronic cervicitis	7	11	8	5	2	0
positive	CIN 1	0	0	1	0	1	0
	CIN 2	0	0	2	0	9	0
	CIN 3	0	0	0	0	0	0
	Ca cx	0	0	1	0	26	0
		0	0	4		36	0
		18		17		38	

Out of total PAP positive cases, 73 -18 were ASCUS, 17 were LSIL and 38 HSIL. None of the ASCUS cases were positive on biopsy all showed chronic cervicitis.

Out of 17 LSIL cases 12 cases were VIA positive and 5 were VIA negative of the 12 cases with VIA positive 8 were negative on biopsy and 4 were positive, with 1 CIN 1,2 CIN 2 and 1 case of invasive ca cx.

Out of 38 cases of HSIL all were VIA positive also 2 cases were biopsy negative and rest 36 cases were positve on biopsy, with 1 case of CIN 1,9 cases of CIN 2 and 26 cases of invasive ca cx. Thus HSIL on pap showed good correlation with invasive Ca cx and high grade CIN.

Table 5: Histopathological correlation of VIA results

Biopsy →	Biopsy –ve	biopsy +ve	CIN 1	CIN 2	CIn 3	Ca cx
VIA +	103	120	54	28	2	36
VIA-	140	3	3	0	0	0
	243	123	53	28	2	36

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Out of 476 VIA positive cases, biopsy was done in 223 cases, and biopsy was positive in 120 cases (true positive) and negative in 103 cases. Out of 120 VIA positive cases 54 cases of CIN 1, 28 cases of CIN 2 and 2 cases of CIN 3 were found while invasive cervical cancer was found in 36 cases 3 cases of VIA -ve had CIN1 on biopsy.

Thus VIA only missed 3 cases of CIN 1 no cases of high grade CION or invasive cervical cancer was missed on VIA in our study.

Table 7: Age correlation of PAP positive cases

Age group	Total screened	PAP positive	Biopsy done	Lost to followup	Biopsy positive
20-30 yrs	510	8(1.48%)	02	5	0
30-40 yrs	545	17(3.1%)	16	1	7 2-CA 3- CIN 2 2-CIN 1
40-50 yrs	540	23(4.2%)	23	0	12 6-CIN 2 6-CA
>50 yrs	195	32(16.4%)	29	3	28 19-CA 3-CIN1 4-CIN2 2-CIN 3
	1790	80	73	7	47

Table 6: Age correlation of VIA positive cases

Age group	Total screened	VIA positive	Biopsy done	Biopsy positive	Biopsy negative
20-30 yrs	510(28.49%)	132(25.88%)	8	4(50%)	4
30-40 yrs	545(30.44%)	131(24.03)	50	17(34%)	33
40-50 yrs	540(30.16)	160(29.6%)	115	60(52.17%)	55
>50 yrs	195(10.8%)	53(27.17%)	50	39(78%)	11
	1790	476	223	120	103

Table 8: Agewise distribution of biopsy positive cases

Age group	VIA +ve	Biopsy done	Biopsy positive	CIN 1	CIN 2	CIN 3	Invasive CA cx
20-30 yrs	132	8	4	2	1	0	1
30-40 yrs	131	50	17	8	7	0	2
40-50 yrs	160	115	60	37	14	0	9
>50 yrs	53	50	39	7	6	2	24
	476	223	120	54	28	2	36

Age of patients screened ranged from 20-80 yrs. As most of these patients had never been screened and came to hospital for first time screening was done even for women above 65 as they came with symptoms.

Out of 1790 patients 510 (28.49%) were in 20-29 yr age group. In this age group 25.88 % VIA positivity was found.132 patients were VIA positive. Most of these patients were young and had active infection and most of these after antibiotic treatment were relieved of symptoms. Biopsy was done for persistence of VIA positivity in 8 cases out of that 4 were positive on biopsy and 4 showed chronic cervicitis of the positive cases 1 was adenocarcinoma of cervix and 2 cases were CIN 1 and 1 CIN 2.

545(30.44%) patients were in 30-39 yr age group .out of that 131 (24.03%) were VIA positive .biopsy was done for 50 cases and it was positive in 17 and in 33 cases it was chronic cervicitis criteria for biopsy positive was CIN 1 and above 8 cases of CIN 1,7 cases of CIN 2 and 2 cases of invasive ca cx were found in this age group.

540(30.16%) were In 40-49 yr age group and out of that 160 (29.9%) were VIA positive. Biopsy done for 115 patients

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and 60 were positive on biopsy and 55 were chronic cervicitis.

37 cases were CIN 1,14 were CIN 2 and 9 cases of invasive ca cx found in this age group.

In this age group majority of patients were in preinvasive stage hence the maximum benefit of screening is in this age group also 9 cases of invasive ca cx were disgnosed in this age group which were in early stage and were treated by radical hysterectomy.

195 patients (10.8%) were more than 50 yrs and of that 53(27.17%) were VIA positive biopsy was done for 50 patients, 3 patients were lost to follow-up 39 (78%) were positive on biopsy with 7 cases of CIN 1,6 cases of CIN 2 and 2 cases of CIN 3.24 cases of invasive cervical cancer were diagnosed .

Hence maximum benfit of screening is in above 30 age group. Below 30 yrs false positive VIA was almost 50% hence overtreatment may be there.

With VIA screening 30 cases of high grade CIN and 36 cases of invasive ca cx were detected .which is quite significant and a total of 54 cases of CIN 1 were also detected.

Table 9: Sensitivity and specificity of VIA as a screening tool

SENSITIVITY	97.56098
SPECIFICITY	57.61317
POSITIVE PREDICTIVE VALUE	53.81166
NEGATIVE PREDICTIVE VALUE	97.9021

The test is highly sensitive but less specific. The test is able to detect 97% of the persons with disease, whereas 43% of the persons test positive for disease which they do not have thus specificity is 57%. About 54% actually have the disease among the people who test positive and for those that test negative 98% do not have the disease.

Table 10: Sensitivity and specificity of PAP as a screening tool

SENSITIVITY	39.16667
SPECIFICITY	89.43089
POSITIVE PREDICTIVE VALUE	64.38356
NEGATIVE PREDICTIVE VALUE	75.08532

Sensitivity and specificity of VIA and PAP calculated. Sensitivity of VIA in our study is 97 % but specificity is 56 %. Positive predictive value of VIA thus is low ie 52.25%. But negative predictive value is very good, about 97 %. Hence VIA test is an ideal screening tool as it is unlikely to miss any lesion esp high grade lesion .but it may overdiagnose hence lead to more no of patients referred or subjected to colposcopy and biopsy.

For PAP test sensitivity is very low it is coming to 39.5% in our study .but specificity was close to 90 %. One more drawback of PAP is lost to follow up as reports are available after 4-5 days and many patients do not come for follow-up hence many positive e cases might be missed .

Comparing both the tests VIA is more sensitive while PAP is more specific.

Discussion

According to the World Health Organization, cervical cancer is the second most common type of cancer among females, and was responsible for over 250,000 deaths in 2005. Approximately 80% of these deaths occurred in developing countries. Cervical cancer continues to be a major public health problem in India with an incidence of 134,420 cases and mortality of 72,825 cases in the year 2008. Without urgent intervention, deaths due to cervical cancer are projected to rise by almost 25% over the next 10 years.[1]

It has been well established that well-organized screening by cytology has substantially reduced the incidence of morbidity and mortality from cervical cancer in developed countries.[2-4]

However, in developing countries like India, universal screening has not been achieved. The main screening method (Pap smear) is available to a small percentage of population. Cytology based screening programmes are difficult to organize owing to limited infrastructure, trained personnel and funds.[5] Many developing countries do not have ample resources to implement cytology-based prevention programs, which necessitates well-organized laboratories to collects material and specialized personnel apt to render a diagnosis.[6] It has been estimated that in India, even with a major effort to expand cytology services, it will not be possible to screen even one-fourth of the population once in a lifetime.[7] Moreover, screening programmes in India are mostly institution based and are restricted to urban centres[8] Thus, in developing countries, there is a need for alternative strategies for early detection of

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premalignant cervical lesions in order to prevent invasive cervical cancer .

Newer approaches such as automated Pap, liquid-based Pap and HPV DNA testing using hybrid capture II (HC II) are time consuming, expensive and not widely available. Prompted by the need for optimal strategies for cervical cancer screening in low-resource settings, the role of visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) has been widely studied in several recent studies, which suggest that VIA and VILI closely match the Pap smear in its performance in detecting cervical cancer precursor.[9]

In a metaanyalsis done by Fahey et al. in 1995[10] involving 62 studies conducted between 1984 and 1992, the mean sensitivity and specificity of cytology was 58% (range 11-99%) and 68% (range 14-97%), respectively. In another recent metaanalysis by Nanda et al. in 2000,[11] the sensitivity of cytology to the detection of CIN 2 or worse lesions ranged from 18% to 98% and the specificity ranged from 17% to 99%. In the IARC multicenter study done in India and Africa by Sankaranarayanan et al. in 2004,[12] which included 11 cross-sectional studies, the sensitivity of VIA ranged from 56.10% to 93.90% and the specificity ranged between 74.20% and 93.80%.

The sensitivity of Pap smear has been found to be lower in developing countries, probably due to the large percentage of inflammatory smears which may mask mild dysplasia.[13] A multi-centric study in India, evaluating the accuracy of conventional cytology, found sensitivity to vary from 37.8-81.3 per cent for ASCUS, 28.9-76.9 per cent for LSIL and 24.4-72.3 per cent for HSIL, between the centre.[14]

In our study the sensitivity of VIA is 97 % while specificity is 57% .and that for PAP is 39 % and 89% respectively

Other authors have reported similar results with VIA having high sensitivity but low or comparable specificity while PAP having low sensitivity but very high specificity.

Author	Sensitivity of VIA	Specificity of VIA
Denny et al [15]	70	79
Cronje et al [16]	79	49
Sankarnarayanan et al[17]	77	86
Goel et al [18]	96	36
Ghosh,Gandhi and Batra et al[13]	89	91
Present study	97	57

Sensitivity and specificity of VIA in various studies

Author	Sensitivity of PAp	Specificity of PAP
Denny et al [15]	40	96
Cronje et al [16]	77	96
Sankarnarayanan et al[17]	65	92
Goel et al [18]	50	97
Ghosh,Gandhi and Batra et al[13]	53	99
Present study	39	89

Considering the various studies, our results of Pap smear as a screening test are comparable. In the present study, the sensitivity of Pap smear was 39 % and the specificity was 89%.

In the present study, the sensitivity of VIA was 97 %, which was better than that of Pap smear, but had a lesser specificity than the Pap smear (Pap 57 % vs. VIA 89%).

The reason behind the high sensitivity and low specificity of VIA in our study could be due to observer bias, more of symptomatic women included in the study as it was an institutional study, all women coming to OPD were screened irrespective of their complaints .

In the present study, the results are in comparison with that of the above-mentioned studies, suggesting that VIA may find a place as an alternative low-resource technology and low-cost method of screening and case finding. As it has very high sensitivity so chances of missing any high grade lesion is remote. While low specificity can be tackled with combining it with another test with high specificity as a second level test before treatment is instituted.

Conclusion

VIA can be used as a screening test for cervical cancer and CIN as it is easy, cheap, quick and simple. Health workers, nurses and paramedics can be easily trained to do the test in peripheral clinics.it does not require any additional

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infrastructure or cost to do the test. Hence can be easily implemented in low resource settings at grass root level.

Population studies are needed to study its usefulness for mass screening .however our results are encouraging and can be implemented atleast in peripheral clinics ,hospitals and institutions by starting a cancer screening clinic and screening all women coming to OPD we can atleast make some difference in reducing morbidity and mortality from advanced cervical cancer.

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