ASSESSMENT OF VISUAL INSPECTION WITH ACETIC ACID (VIA) AS A SCREENING TEST FOR CERVICAL NEOPLASIA IN COMPARISON WITH CYTOLOGIC SCREENING

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Abstract- This study has been designed to compare visual inspection of cervix with acetic acid (VIA test) with cytology as an accepted method for screening of cervical carcinoma and its precursors. 1200 eligible women were examined by both Pap-smear and VIA tests in Imam Khomeini Hospital, a referral general hospital in Tehran, Iran. Those who had abnormal results in one or both of the screening tests (n = 308) and those who had clinically suspicious lesions even if the tests were negative in addition to 10% of otherwise normal patients with negative tests (totally 290 patients) were referred for colposcopy and biopsy if mandated. From 598 patients who were introduced to colposcopy services, 355 patients required biopsies or endocervical curettage (ECC). Those with CIN I or worse lesions diagnosed by histology were considered true-positive. VIA results were positive in 191 women (16.1%) and cytology was abnormal (for ASCUS or worse lesions) in 226 women (19%). VIA and cytology detected 130 (74%, 95% CI: 68%-81%) and 126 (72%, 95% CI: 65%-79%) cases respectively, yielding a sensitivity ratio of 1.03. VIA detected 31 lesions which were cytologically negative and cytology detected 27 lesions which were negative by VIA; 18 cancerous and precancerous lesions were missed in both modalities. The approximate specificities of VIA and cytology were 94% (95% CI: 93%-95%) and 90.2% (95% CI: 88%-92%) respectively. Also, the positive predictive values were 68.1% (95% CI: 61%-75%) and 55.7% (95% CI: 49%-62%) respectively. These results indicate that VIA and cytology had very similar performance in detecting CIN I or worse lesions in this study.
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Key Words: Cervical carcinoma, Visual Inspection with Acetic Acid (VIA), Pap-smear, Screening, Colposcopy

INTRODUCTION

All over the world, cervical carcinoma is the second most common cancer in females after breast cancer (1,2), and in developing countries is considered as the most fatal malignancy in women (2). During the last 40 years, mortality due to this cancer has been reduced significantly in developed countries and that is because of screening tests such as Pap-smear. Despite the reduction, this disease is still one of the most important causes of mortality in women especially in developing countries (3-5). Performing Pap-smear repeatedly for screening cervical cancer needs availabilities such as laboratories, expert specialists and affording expenses for such a procedure. Establishing such possibilities in developing countries is not always feasible (6). As such, in Iran for the lack of quality control in remote areas, screening patients has a low quality, besides high expenses and lack of enough patients' education makes patients not referring to medical centers for screening or its continuance. Also in Iran, we have more than 30% false negative results (7) so we are greatly in need for a cheaper, handy and precise test for screening patients. One of these tests that has been introduced as a substitute or complementary to cytology test for diagnosing cervical cancer is visual inspection with acetic acid (VIA test). In a study by Sankaranarayanan and associates, 3000 women underwent screening tests. 298 (9.9%) had positive VIA test and 307 (10.2%) abnormal Pap-smear tests. In 102 of these patients, both of these tests were positive. Sensitivity of VIA test was estimated as 90.1% and its specificity was 92.2% and its positive predicting value was about 17%. These numbers were 86.2%, 92.7% and 17.2% in Pap-smear tests respectively (8). Other studies reported that VIA test results in developing countries could be compared to Pap-smear results and could be recommended as a substitute for it. This test could be used as a complementary to the cytology test. In these studies

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sensitivity of VIA test was estimated about 60-70% and relative specificity of it was about 70% (9-11). In regard to these studies and their results, we decided to perform these screening tests, VIA and Pap-smear, on 1200 women who were referred to Imam Khomeini Hospital clinic to evaluate and compare the results.

MATERIALS AND METHODS

This research has been performed as a diagnosing test study. Cases had been chosen from non-virgin women who were referred to Imam Khomaini Hospital Ob-Gyn clinic during 1999-2001. Inclusion criterion was patient's consent and exclusion criteria were virginity, being in menstrual period, to have not uterine abnormal uterine bleeding for any cause, hysterectomy or wedge resection and diagnosed cervical cancer. Sample size estimated 1200 patients by considering 60% sensitivity for VIA test to diagnose CIN I and higher lesions, 95% confidence interval, 10% power and estimated 8% abnormal Pap-smear test, in under study population. Sampling was non-randomized and from all available patients who were at hand and till completion of sample size.

All women were being informed about the procedure and after cervical examination, Pap-smear and VIA tests were performed. Physicians who tested VIA didn't know the results of Pap-smear and after washing cervix with acetic acid for 30-60 seconds, inspection for finding lesions under proper light were done. VIA test had been considered positive when Aceto-White reaction could be seen clearly. Abnormal Pap-smear test was applied to Atypical Squamous Cells of undetermined Significance (ASCUS) lesions or more. These two tests were performed by four of center's senior Ob-Gyn residents who were briefed clearly regarding comprehending the tests. If any one of these two tests was abnormal, then that patient would be referred to attending for further survey by means of colposcopy. Besides, those who had an abnormal gross appearance of cervix and when we were suspicious, were sent for colposcopy. Also we sent 10% of our patients with negative Pap-smear or negative VIA test to colposcopy after receiving their consent. Based on colposcopy result and if it was normal and satisfactory the test was considered negative and if it was abnormal or unsatisfactory then biopsy or endocervical curettage (ECC) was done. Cytology slides and samples of biopsies and ECC were referred to central pathology laboratory in the hospital and surveyed by senior pathology residents under their attendings' supervision. If histologic study reported lesions as CIN I or higher, test would have been considered positive statistically.

Interval between performing screening tests and colposcopy was 1-50 days. Because of some ethical limits we could not perform biopsy in all cases, and also because of ethical and economical limitations in performing colposcopy, there was no way to estimate sensitivity or specificity of these tests directly. But with the help of some parameters we could do it approximately:

1- Detection rate of CIN I lesions or higher (based on biopsy); this rate can be calculated by dividing detected cases that were under study.

2- Sensitivity ratio between these two tests; which can be calculated by dividing detection rate for VIA test to detection rate of Pap-smear test. A ratio number more than one could show higher sensitivity for VIA test.

3- Purpose to estimate specificity; those that had negative results by screening tests but except those who had positive biopsies, were considered as true negatives. By subtracting true positive cases (by biopsy) from all screened patients we found our whole negative cases and so to divide true negative cases to these cases we had our approximate specificity.

4- Positive predictive value (PPV) which is calculated by dividing true positive detected cases (in each of the screening tests) to all positive cases in that test.

Analysis of data was performed by SPSS (version 10) and for calculating sensitivity, specificity and positive predictive value we considered 95% as our confidence interval. To find relations between variables we used Chi-square test, Fisher's exact test by considering a= 0.05.

RESULTS

1200 women had an age spectrum between 17 and 88, with 42.1 years mean (SD: 12.1). All other specifications can be found in Table 1.

Cervical appearance without magnification was normal in 331 of the patients. 635 had lesions such as red spots, inflammation, polyps, ectropions and cervicitis and 176 of these patients showed lesions such as polyps and erosion. In 15 of them suspicious cancerous lesions were observed. Analysis data was performed based on data which were available from 1190 women. We had 191 (16.1%) positive VIA tests

and 226 (19%) abnormal Pap-smear tests which had ASCUS or worse lesions (109 of these had both positive tests) (Table 2).

Table 1. Specifications of patients who underwent screening tests (VIA and Pap-smear) in Imam Khomeini Hospital during 1999-2001

Specifications	N = 1200 (%)
Age:	
<20	13(1.1%)
20-29	151(12.6%)
30-39	352(29.3%)
40-49	399(33.2%)
50-59	163(13.6%)
60-69	84(7.0%)
≥ 70	30(2.5%)
Unknown	8(0.7%)
Mean age of starting of menstruation (years)	13.8 (SD: 1.6)
Mean age of marriage (years)	18.3 (SD: 4.3)
Mean age of menopause (years)	46.7(SD: 4.6)
Parity:	
0	31(2.6%)
1-5	786(65.5%)
6-10	325(27.1%)
≥ 11	37(3.1%)
Unknown	21(1.7%)

All women who had positive VIA or abnormal Pap-smear tests (308 patients) were referred for colposcopy. Also those who had no positive or abnormal tests but had suspicious lesions in their non-magnified cervical appearance and about 25% of the others (in whole 290 patients) were referred to undergo culposcopy. From 598 performed colposcopy procedures, 355 (54.9%) had abnormal or unsatisfactory findings which for these reasons biopsy and ECC were done for them. Histopathologic results of these procedures can be found in Table 3.

From 175 women with positive biopsy, 130 were detected by VIA yielding a detection rate of 109.2 per 1000. Sensitivity was about 74.3% (95% CI: 68-81%). Pap-smear was detected in 126 of them with a detection rate of 105.9 per 1000 and a sensitivity of about 72% (95% CI: 65-79%). Sensitivity ratio between these two tests was estimated as 1.03. In 99 (56.6%) of cases both the tests were abnormal. VIA detected 31 lesions (21 CIN I, 6 CIN II, 3 CIN III and one invasive carcinoma) missed by cytology whereas the cytology detected 27 lesions (18 CIN I, 4 CIN II, 2 CIN III and 3 invasive carcinoma) missed by VIA (Table 4). Among 290 women which had negative screening tests and referred to for colposcopy, 129 (44.5%) biopsies were performed which detected 18 lesions (11 CIN I, 6 CIN II and one CIN III). Whereas VIA resulted in the detection of 82.4% (14 of 17) of invasive carcinoma, cytology detected 94.1% (16 of 17).

88.9% of CIN III, 76.7% of CIN II and 67% of CIN I were detected by VIA. These figures were 85.2%, 72.1% and 63.6% for cytology, respectively. Both tests missed 3.7% CIN III, 14% CIN II and 12.5% CIN I. Approximate specificity of VIA test was 94% (95% CI: 93-95%) and for Pap-smear it was 90.2% (95% CI: 88-92%). PPV of these two tests were 68.1% (95% CI: 61-75%) and 55.7% (95% CI: 49-62%) respectively. When VIA and Pap-smear are considered as parallel screening tests, then sensitivity and specificity would be 89.7% and 85.1% respectively (Table 5).

Table 2. Screen tests findings of patients that were referred to Imam Khomeini Hospital during 1999-2001

VIA	Abnormal Pap-smear	No:	Refer to colposcopy	Normal and satisfactory colposcopy	In need of biopsy or endocervical curettage
+	+	109	109	4	105
+	-	82	82	16	66
-	+	117	117	62	55
-	-	882	290	161	129
		1190	598	243	355

Table 3. Distribution of histopathological findings based on screen tests findings of patients that were referred to Imam Khomeini Hospital during 1999-2001

VIA	Abnormal Pap-smear	No.	Positive biopsy				Negative biopsy	
			CIN I	CIN II	CIN III	Invasive Carcinoma	Metaplasia	Normal
+	+	105	38	27	21	13	6	0
+	-	66	21	6	3	1	34	1
-	+	55	18	4	2	3	27	1
-	-	129	11	6	1	0	102	9
		355	88	43	27	17	169	11

Table 4. Distribution of histopathological findings based on screen tests findings of patients that were referred to Imam Khomeini Hospital during 1999-2001, if we considered Pap-smear report LSIL or higher

VIA	Abnormal Pap-smear	No.	Positive biopsy				Negative biopsy	
			CIN I	CIN II	CIN III	Invasive Carcinoma	Metaplasia	Normal
+	+	51	14	13	13	9	2	0
+	-	120	45	20	11	5	38	1
-	+	23	9	3	1	3	6	1
-	-	161	20	7	2	0	123	9
		355	88	43	27	17	169	11

Table 5. Validity of screening tests for patients that were referred to Imam Khomeini Hospital during 1999-2001

	Sensitivity	Specificity	PPV*	NPV**
	95% CI			
VIA	74.3%	94%	68.1%	95.5%
	(68 - 81)	(93 - 95)	(61 - 75)	(94.2 - 96.8)
Pap-smear(1)	72%	90.2%	55.7%	94.9%
	(65 - 79)	(88 - 92)	(49 - 62)	(93.5 - 96.3)
VIA & Pap-smear as	89.7%	85.1%	51%	98%
parallel tests(1)	(85 - 94)	(83 - 87)	(45.4 - 56.6)	(97.0 - 98.9)
Pap-smear (2)	37.1%	97.9%	75.6%	90%
	(30 - 43.3)	(97.1 - 98.8)	(66.5 - 84.7)	(88.3 - 91.8)

(1) Based on ASCUS or worse lesion are positive

(2) Based on LSIL or worse lesion are positive

* Positive Predictive Value

** Negative Predictive Value

If we consider SIL or more intense lesions as abnormal Pap-smear, then we will have 86 (7.2%) abnormal Pap-smear tests and based on this, sensitivity of this test would be 37.1% (95% CI: 30-43.3%), its specificity 97.9% (95% CI: 97.1-98.8%) and its PPV 75.6% (95% CI: 66.5-84.7%) (Table 5). Based on these calculations Pap-smear would not be able to recognize 65 CIN I, 27 CIN II, 13 CIN I, and 5 invasive carcinoma. In other words, the sensitivity of cytology for these lesions would be 24.2%, 37.2% and 51.9% respectively, and the sensitivity for invasive carcinoma would be 70.6%.

Table 6. Validity of VIA and Pap-smear in some studies

	Sensitivity	Specificity	PPV*
Sankaranarayanan, et al. 1998 (1)			
VIA	90.1%	92.2%	17%
Pap-smear	86.3%	92.7%	17.2%
Sankaranarayanan, et al. 1997 (9)			
VIA	95.8%	-	-
Pap-smear	62%	-	-
Gaffikin et al. 1997 (10)			
VIA	60 - 70%	70%	-
Cohn et al. (12)			
VIA	76.7%	64.1%	-
Pap-smear	44.3%	90.6%	-

* Positive Predictive Value

DISCUSSION

In this study we compared VIA test as a screening test to detect cervical malignancies and its precursors with Pap-smear test. From 1190 cases, 191 (16.1%) were VIA positive and 226 (19%) had abnormal Pap-smear test (ASCUS or more). If we consider LSIL (CIN I) and higher as abnormal Pap-smear we only had 86 (7.2%) patients with abnormal Pap-smear. In Sankaranarayanan et al. study 9.9% of patients had VIA positive and 10.2% abnormal Pap-smear (Atypical and more) (1). In another study in India and on 1351 patients, Positive VIA and abnormal Pap-smear were 37.5% and 15.2% respectively (9). Differences in those populations might be the reason for these differences in the results of the tests. Imam Khomeini is a referral hospital so it might be acceptable if we consider our patients as a high risk population and so there would be more abnormal screening test results compared to general population. VIA test compared to Pap-smear had a higher value as regards sensitivity, specificity and PPV in our study. Its sensitivity was 74.3% (95% CI: 68-81%) compared to Pap-smear with 72% (95% CI: 65-79%), but to consider confidence interval there had been no statistically significant difference. Sensitivity ratio was 1.03. Specificity of VIA was 94% (95% CI: 93-95%) and for Pap-smear, this was 90.2% (95% CI: 88-92%) but by considering confidence interval there had been no statistically significant difference. PPV of these tests were 68.1% (95% CI: 61-75%) and 55.7% (95% CI: 49-62%) which showed a significant difference.

In Sankaranarayanan et al. study, VIA sensitivity was 90.1% and for Pap-smear it was 86.3% with no significant difference. Sensitivity ratio was 1.05. Specificities of these tests were 92.2% and 92.7% respectively with no significant difference. PPV of these were 17% and 17.2% (1). Findings of othger studies are shown in Table 6.

Higher PPV in our study compared to Sankaranarayanan et al. study is because of our population that comprised high risk patients. thus we had more positive biopsies. In our study VIA detected 14 out of 17 invasive carcinoma versus 16 out of 17 for Pap-smear, but the ability of VIA in recognizing CIN lesions (I, II and III) was higher. There was no invasive carcinoma by these tests not recognized, but 11 cases of CIN I, 6 CIN II and 1 CIN III (18 in whole) had been unrecognized. VIA diagnosed 34 cases of metaplasia and Pap-smear recognized 27 of them. If VIA and Pap-smear are going to run parallel as screening, then sensitivity would increase as high as 89.7% (157 from 175) and specificity would be 85.1%. Based on these, PPV might be 51%. In regard to validity of tests, we can say that false positive rate for VIA was 6% and for Pap-smear 9.8% and if we used both of them as screening tests simultaneously this rate would increase to 14.9%. So, VIA test is more proper for diagnosing cervical carcinoma and there would be less unnecessary colposcopies and biopsies. In a study from Zimbabwe, weakness of VIA test was reported due to its high false positive results (35.9%) as a cause of referring patients for unnecessary colposcopy and entailing more expenses (6). If we considered LSIL and more advanced lesions for abnormal Pap-smear test, sensitivity of this test would have been much lower (37.1%) and could find

only 65 true positive patients. Sixty one cases with ASCUS report had positive biopsies (32 CIN I, 15 CIN II, 9 CIN III and 5 invasive carcinoma). Cohn and Herzog have reported that 7% of women whom their Pap-smear results were ASCUS, HSIL histology and cancer would report (12). Monsoneyo and et al. recommend that it would be better to consider ASCUS and more advanced lesions as threshold for doing colposcopy (13). Aisner and associates explained in their study that proper screening test for cervical cancer had to recognize lesions with higher risk in changing to malignancy with more sensitivity (compare to lesions with less potential to change into malignancy) (14). VIA test shows such specifications in our study. Except for invasive carcinoma in which the sensitivity of Pap-smear was higher, in others (CIN I, CIN II and CIN III) sensitivity of VIA was higher. Based on results of this study, it seems that VIA test has the proper characteristics of being screening test to diagnose malignancies of cervix. VIA test may be used not only as a substitute for Pap-smear screening test in areas where it is not available but also as a complementary for lessening of false negative results of Pap-smear where this test is at hand. It should be known that by doing it, false positive results would be greater and so more cases for colposcopy, we should consider and evaluate their cost effectiveness and risk of missing a malignancy in a patient if we don't perform these tests.

REFERENCES

1. Sankaranarayanan R, Wesley R, Somanathant T, et al. Visual inspection of the uterine cervix after the application of acetic acid in the detection of cervical carcinoma and its precursors. Cancer, 1998 Nov; 83(10): 2150-2156.

2. Blumenthal PD, Gaffikin L, Chirenje ZM, et al. Adjunctive testing for cervical cancer in low-resource settings with visual inspection, HPV, and the Pap-smear. Int J Gynaecol Obstet, 2001 Jan; 72(1): 47-53.

3. Moss TR. Cervical cytology and colposcopy in young patients attending genitourinary medicine clinics: invalid intrusion or preventive opportunity and definitive audit? Cytopathology, 1999 Feb; 10(1): 2-7.

4. Solar ME, Gaffikine L, Blumenthal P. Cervical cancer screening in developing countries primary care update. Ob Gyn, 2000; 7(3): 118-123.

5. Hall AJ. Cervical screening: technology, treatment, policy– what is appropriate? Trop Med Int Health, 2000 Dec; 5(12): 835-836.

6. Berek JS, Adashi EY, Hillard PA. In: Novak's Gynecology (12th ed.) by Williams and Wilkins, 1996.

7. Eftekhar Z, Yarandi F, Moosavi A, et al. Accuracy of acetic acid 5% in early detection of cervical dysplasia. The Iranian Journal of Obstetrics, Gynecology & Infertility, 2000; 1(4): 9-13.

8. Frisch LE, Milner FH, Ferris DG. Naked eye inspection of the cervix after acetic acid application may improve the predictive value of negative cytologic screening. J Fan Pract 1994 Nov; 39(5): 457-460.

9. Sankaranarayanan R, Syamalakunary B, Wesley R, et al. Visual inspection as a screening test for cervical cancer control in developing countries. In: Franco e, Monsonego J. Developments in cervical cancer screening and prevention. Blackwell Sciences, Oxford 1997; P: 411-421.

10. Gaffikin l, Blumenthal PD, Davis C, Griffey Brechin SJ. Workshop proceedings: alternatives for cervical cancer screening and treatment in low-resource settings. By: JHPIEGO Co. Baltimore 1997.

11. Megavand E, Denny L, Dehaeck K, et al. Acetic acid visualization of the cervix: an alternative to cytologic screening. Obstet Gynecol, 1996 Sep; 88(3): 383-386.

12Cohn DE, Herzog TJ. New innovations in cervical cancer screening. Clin Obstet and Gynecol, 2001 Sep; 44(3): 538-549.

13. Monsonego J. Role of HPV testing in secondary and primary screening of cervical Neoplasia. Journal of Lower Genital Tract Disease 2000; 4(2): 108-113.

14. Aisner S, Austin RM, Bishop J, et al. Procedures used in the creation of the American society of cytopathology: cervical cytology practice guidelines. Journal of Lower Genital Tract Disease, 2001; 5(3): 159-184.