

Visual inspection using acetic acid and pap smear as a method of cervical cancer screening

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Introduction: The objective of this study was to study the of comparison of visual inspection using acetic acid and pap smear as a method of cervical cancer screening. The specific objectives were to determine the proportion of women screened positive with VIA and proportion of women screened positive with pap smear. Another specific objective was to determine total number of cervical intra-epithelial neoplasia and carcinoma cervix in the study population.

Method: This was a comparative study. A total of 500 women presenting to the outpatient gynecologic clinic, T.U. Teaching Hospital from 23rd February 2004 to 22nd February 2005, who met the inclusion criteria were examined by both conventional cytology and visual inspection using 5% acetic acid. Distinct acetowhite areas touching the transformation zone were categorized as VIA positive cases. ASCUS or worse lesions by cytology were considered as positive smears. Those women who showed positive test result with either VIA or pap smear or both tests were further subjected to colposcopy directed biopsy and histology was taken as gold standard to compare the performance of VIA and cytology. Those for whom histology revealed no pathology or reactive/reparative change or inflammation were considered as false positives.

Results: On VIA, 37 out of 500 women screened had acetowhite lesions. On pap smear, 27 out of the 500 women had ASCUS or worse lesions. The proportion of women screened positive with VIA was 7.4 % and the proportion of women screened positive with pap smear was 5.4 %. Of the 500 enrolled women, 20 were positive on both VIA and cytology; 17 were positive on VIA only; and 7 were positive on cytology only. So 44 patients had cervical biopsies performed on them.

Histological diagnosis of CIN/cancer was made in 28 out of the total 44 patients who underwent biopsy. Incidence of CIN/ cancer cervix in the study population was found to be 5.6 %. Pap smear picked up 20 out of the 28 biopsy-proven cases. The 8 lesions missed by cytology included 5 low grade, 2 high grade and 1 cancer. VIA could identify 27 out of the 28 CIN/carcinoma cervixes; the only lesion being missed was LSIL. But VIA had higher number of false positives as compared to cytology. VIA was more sensitive (96.4 %) than pap smear (71.4%), which was statistically significant. However, the specificity of VIA was lower (37.5 %) than that of cytology (56.3 %). The PPV of VIA was 73% versus 71.4 % for pap smear. The NPV of VIA was 85.7 % versus 52.9 % for cytology. Overall, VIA demonstrated an accuracy of 75 % as compared to 65.9 % for cytology.

Conclusion: In women undergoing screening for pre-invasive and cancer cervix, visual inspection using 5 % acetic acid was found to be more sensitive and has a higher accuracy as compared to pap smear. VIA is less specific than cytology, resulting in high false-positive and hence unnecessary referral for colposcopy/biopsy. Although the present study is small, other larger comparative studies have evaluated the validity of VIA as a method of cervical cancer screening and concluded the same. Another important feature of VIA is its high Negative Predictive Value, which means that when the test result is negative, the woman can go home assured that she is not likely to have a neoplastic cervical lesion. Visual inspection is a simple, accurate, cost effective method of rapidly differentiating between a potentially diseased cervix and a healthy one and therefore its use can be recommended as primary screening method.

Introduction

Cancer of cervix is the second most common cancer of woman worldwide after cancer of the breast and the commonest in developing countries.¹ The worldwide incidence of cancer cervix in terms of 100,000 women-years is 16.1 and the death rate is 8. In Asian subcontinent, the incidence is even more and reported to be 26.5 and the death rate being doubled to 15.¹ In spite of being such a major health problem in developing countries, cervical cancer screening programmes are small scale or non-existent. Consequently, there are few opportunities to diagnose precancerous lesions and most patients present with invasive disease at an advance stage. Over the years, pap smear based cytology screening has been practiced. In less-developed countries, provision for pap smear is available, but usually only in urban areas or in the private health sector that serves a small proportion of the female population. Pap smear requires technical capabilities, communication, follow up and training- beyond the capacity of healthcare infrastructure in many of the developing countries. Further more, such screening may not be available at the grass-root level of the community. Thus, other methods of cervical cancer screening have been investigated. One such method is unmagnified naked eye visual examination of uterine cervix after application of 5% acetic acid, termed "VIA". VIA was first reported by Ottaviano and La Torre in 1982, that visual inspection with acetic acid could identify abnormal acetowhite changes.² The principle behind aceto-whitening: acetic acid causes dehydration of cells and coagulation of cellular protein; thereby reducing the transparency of epithelium that appears white. These changes are more pronounced in abnormal epithelium because of higher concentration of proteins (increase nuclear protein and chromatin material) in the dysplastic cells.³ It is possible to recognize acetowhitening of the dysplastic cervical epithelium with the naked eye, and this constitutes a positive VIA test.² VIA involves inserting a vaginal speculum; swabbing the cervix with 5% acetic acid solution and observing the squamocolumnar junction. Normal squamous epithelium is light pink in colour and the columnar epithelium is red. CIN lesion, if present will appear as a dense-white opacity that abuts the squamocolumnar junction and this constitutes a positive test result (International Agency for Research on Cancer).⁴ The acetowhite appearance is not unique to CIN and cancer. It is also seen in other conditions when increased nuclear protein is present; as in healing and regenerating epithelium (associated with inflammation and erosion), immature squamous metaplasia and leucoplakia. But such inflammatory acetowhitening are patchy, ill defined, not

restricted to the transformation zone and quickly disappear (within a minute). On the other hand, the acetowhite of CIN is dense and opaque with well-demarcated margins and occupies the transformation zone. The opaque whitening in CIN appears instantaneously and reverses much more slowly, lasting for 3-5 minutes.⁴

Study design

To evaluate the validity of visual inspection of cervix using acetic acid, a descriptive study was conducted in the Out-Patient Department of Obstetrics and Gynecology, T.U. Teaching Hospital from 23rd February 2004 to 22nd February 2005. The objective of this study was to study the of comparison of visual inspection using acetic acid and pap smear as a method of cervical cancer screening. 500 eligible women who met the inclusion criteria were examined by both conventional cytology and visual inspection using 5% acetic acid. Distinct acetowhite areas touching the transformation zone were categorized as VIA positive cases. ASCUS or worse lesions by cytology were considered as positive smears. Those women who showed positive test result with either VIA or pap smear or both tests were further subjected to colposcopy directed biopsy and histology was taken as gold standard to compare the performance of VIA and cytology. Those for whom histology revealed no pathology or reactive/reparative change or inflammation were considered as false positives.

Results

On VIA, 37 out of 500 women screened had acetowhite lesions. On pap smear, 27 out of the 500 women had ASCUS or worse lesions. The proportion of women screened positive with VIA was 7.4 % and the proportion of women screened positive with pap smear was 5.4 %. Of the 500 enrolled women, 20 were positive on both VIA and cytology; 17 were positive on VIA only; and 7 were positive on cytology only (*Table 1*). So 44 patients had cervical biopsies performed on them. Histological diagnosis of CIN/cancer was made in 28 out of the total 44 patients who underwent biopsy (*Table 2, 3*). Incidence of CIN/ cancer cervix in the study population was found to be 5.6 %. Pap smear picked up 20 out of the 28 biopsy-proven cases. The 8 lesions missed by cytology included 5 low grade, 2 high grade and 1 cancer. VIA could identify 27 out of the 28 CIN/carcinoma cervixes; the only lesion being missed was LSIL. But VIA had higher number of false positives as compared to cytology. VIA was more sensitive (96.4 %) than pap smear (71.4%), which was statistically significant. However, the specificity of VIA was lower (37.5 %) than that of cytology (56.3 %). The PPV of VIA was 73% versus 71.4 % for pap

smear. The NPV of VIA was 85.7 % versus 52.9 % for cytology (Fig. 1). Overall, VIA demonstrated an accuracy of 75 % as compared to 65.9 % for cytology.

Characteristics of women who underwent screening tests

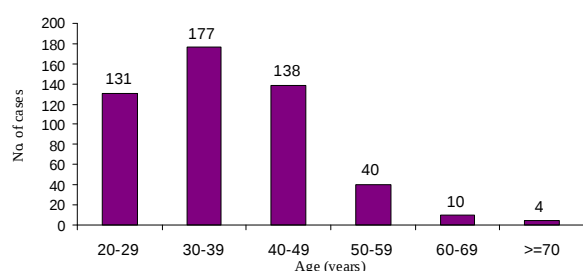


Fig. 1. Age distribution

Maximum number of women were in the age group of 30-39 years (35.4 %), followed by 40-49 years (27.6 %), then 20-29 years (26.2 %) (Fig. 1 and Table 4).

Table 1. Outcome of cytology (n= 500)

Pap smear	No.	Percentage
Normal/Inflammation	473	94.6 %
ASCUS/ASGUS	5	1 %
LSIL	6	1.2 %
HSIL	15	3 %
Carcinoma	1	0.2 %
TOTAL	500	100 %

Table 2. Number of cervical biopsies performed (n=44)

Test Outcome	Number
Both VIA & Pap smear positive	20
Only VIA positive	17
Only Pap smear positive	7
Total	44

Table 3. Biopsy outcome (n=44)

Histopathology	Number	Percentage
Normal/ Cervicitis	16	36.4 %
LSIL	11	25 %
HSIL	8	18.2 %
Carcinoma	9	20.4 %
Total	44	100 %

Table 4. Characteristics of study population

CHARACTERISTICS		
Mean age of women	36.7 years	Range 20- 72 years
Mean age at menarche	13.9 years	Range 12- 18 years
Mean age at marriage	18.1 years	Range 5- 38 years
Mean age at 1 st pregnancy	19.7 years	Range 14- 38 years
Mean age at last pregnancy	27.4 years	Range 22- 45 years
Women in reproductive age	437	87.4 %
Women attained menopause	63	12.6 %
Mean age at menopause	46 years	
Mean parity	3.4	Range 0- 13
Clinically healthy cervix	147	29.4 %
Grossly unhealthy cervix	353	70.6 %

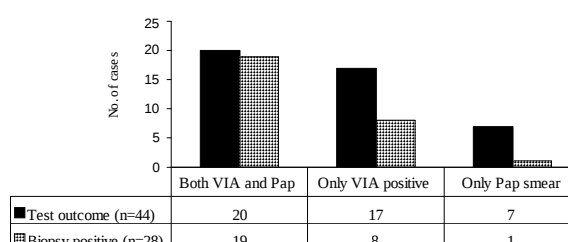


Fig. 2. Test outcome and biopsy proven true disease

Discussion

The proportion of women screened positive with VIA in the study is 7.4 %. Using a similar criteria like ours (distinct acetowhite areas touching the transformation zone to define positive test outcome); a proportion of 6.6 % was observed by El Shalankany A⁵, 9.9 % by Shankaranarayanan et al⁶ and 12.5 % Goel A⁷. However unlike the present study when all grades of acetowhiteness was considered positive, a higher proportion of women were found to be VIA positive; as was reported by Belinson⁸ (28 %), Doh AS⁹ (21.7 %) and Ghaemmaghami¹⁰ (16.1 %). The wide variation (6-28%) in positive rates in the various studies is due to the different criteria used for defining VIA test positivity. This fact is well demonstrated by Shankaranarayanan et al¹¹ who found 15.8 % positive with high threshold VIA (distinct acetowhite lesion on squamocolumnar junction) versus 24.2 % with low threshold VIA (any white lesion) when the test was performed on 4,444 recruits. So whenever a study is undertaken, the definition used for categorization of “VIA positive” will have a direct impact on sensitivity and specificity outcome. Hence, it is an urgent priority to

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establish standard definition and approach for VIA result to avoid variation in the way it is interpreted.¹¹

Regarding accuracy of conventional cytology, the sensitivity of a single pap smear is reported to be between 60% and 80%.¹² In a meta-analysis of 62 studies of cytology, conducted between 1984 and 1992 the mean sensitivity was found to be 58% and mean specificity 68%.¹² Nanda K et al¹³ in another meta-analysis involving 94 studies, showed that sensitivity of pap smear ranged from 18% to 98%; the specificity ranging from 17% to 99%. Authors showed that among these all studies, the 12 studies with the least bias estimated sensitivity range from 30% to 87% and specificity range from 86% to 100%. It is recognized that difficulty in performing the different steps accurately and the lack of quality control in cytology screening are the main causes of its sub-optimal sensitivity. Gupta S, Sodhani P¹⁴ carried out a study to analyze the factors that hamper with the diagnosis of high-grade lesions by cervical cytology. Cervical smears of one hundred histology proven cases of CIN III were retrieved and reviewed to study cytology agreement in the diagnosis of high-grade lesions. It was concluded that the major confounding factors responsible for under-interpretation on cytology included air drying artifacts (sampling error) and metaplastic maturation of abnormal cells.

In a workshop, a review of results from several cross-sectional studies (from the year 1982-2002) investigating the performance of VIA has suggested sensitivity ranged between 66- 96% and specificity between 64- 98%.¹⁵

With regards to comparison of visual inspection and cytology, our results are consistent with recent studies that have shown that VIA is more sensitive but less specific than cytology.^{5,7,9,16-19}

Conclusion

In women undergoing screening for pre-invasive and cancer cervix, visual inspection using 5 % acetic acid was found to be more sensitive and has a higher accuracy as compared to pap smear. VIA is less specific than cytology, resulting in high false-positive and hence unnecessary referral for colposcopy/biopsy. Although the present study is small, other larger comparative studies have evaluated the validity of VIA as a method of cervical cancer screening and concluded the same. A high Negative Predictive Value of VIA warrants particular mention. In places characterized by increased incidence of cervical cancer and its precursors, use of VIA as a “primary screening” means that the women assessed as test-negative would be reassured that most probably they do not have such lesions. Where large-scale pap smear screening is not available, VIA can be a

established as a sustainable modality for testing of cervical pre-cancerous lesions. VIA is a simple, accurate, cost effective method of rapidly differentiating between a potentially diseased cervix and a healthy one and therefore its use can be recommended as primary screening method as an alternative to cytology.

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