Original article:

Comparative study of cytology versus colposcopy to evaluate women who are positive on visual inspection test in rural medical college Bangalore

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Abstract:

Introduction: Colposcopic evaluation and guided biopsy is an important diagnostic step and standard of management for abnormal cytology smears in developed countries. The present study evaluates the performance of colposcopy vs conventional cytology in estimating the presence and grade of cervical disease against the reference standard of histopathology as a secondary test modality to triage women found positive on primary screening by visual inspection with 5% acetic acid (via).

Study Design: colposcopy and directed biopsy were performed after primary screening for cervical cancer in mvj medical college bangalore , india. Healthy women (7794) in the age group of 35-70 years participated in the cervical cancer early detection program in the hospital and community cancer screening clinics. women found positive on the primary screening test by via underwent diagnostic evaluation by pap smear cytology and colposcopy evaluation with directed biopsies. Accuracy parameters and their 95% confidence intervals were calculated using 2 χ 2 tables and standard formulae.

RESULTS: Agreement between colposcopic impression and colposcopy directed biopsy,sensitivity - 57.14% specificity- 93.45% ,ppv -39.77% ,npv -96.64%. agreement between cytology and colposcopy directed biopsy. sensitivity - 49.20%specificity- 97.41%ppv- 59.04%npv- 96.20%

CONCLUSION: Colposcopy is a good sensitive test and can be considered as a secondary testing tool to triage women found positive on via.

Introduction

India has a disproportionately high burden of cervical cancer [1]. 126,000 new cases of cancer cervix are added and 71,000 patients die annually due to the disease.[2] Cervical cancer is preventable, but most women in poorer countries do not have access to effective screening programmes. The difficulties in implementing an organized cervical cytology screening in India and other low-resource countries have prompted several Indian researchers to evaluate affordable and effective alternative screening approaches to facilitate evolution and implementation of cost-effective screening in due course .[3] The difficulties and resource constraints in introducing cervical cytology screening programs and the sub-optimal performance of Pap smear screening in less developed countries have encouraged the evaluation of visual inspection with 3–5% acetic acid (VIA) as an alternative screening method. VIA meets the criteria of a good screening test, the test itself is simple to administer, and the assessment results are immediately available. VIA involves visually examining the cervix for lesions with the naked eye no magnification after the application of a 3-5% acetic acid wash [4.] Recent studies indicate that it has a sensitivity ranging from 70 to 85% in detecting high-grade cervical intraepithelial neoplasia (CIN 2–3) and invasive cancer; its specificity ranges from 67

to 85% [5]. Low specificity has been its limitation, which would result in excessive referrals and treatment of false-positive lesions subsequently increasing the referral load as well as the cost of unnecessary treatment on the health system. Thus, determining which women with positive VIA-based tests are at risk for significant cervical disease, performing appropriate diagnostic workups, and treating cancer precursors presents a major public health challenge.

Several studies have considered human papillomavirus (HPV) testing and repeat cytology as a triage method for women with atypical squamous cells of unknown significance (ASCUS). [6,7] But these triage modalities are not feasible in a developing country such as India. Cervical cytology screening programs despite its history of success in cancer screening has important limitations, particularly its high false-negative rate, which carries important public health implications. [8]

Colposcopic evaluation and guided biopsy remains a critical diagnostic step for women with squamous intraepithelial lesions to identify women who require treatment.[9]

Thus, in the context of adopting VIA-based approaches, namely VIA as a primary screening modality in low-resource settings, we tried to evaluate the performance of colposcopy in estimating the presence and grade of cervical disease vs conventional cytology testing as a secondary test modality to triage women found positive on VIA test. Colposcopy may then be used to identify women who are likely to benefit from immediate treatment.

Materials and methods

The study was conducted in MVJ medical college and research hospital and health centers attached to the college. Instituitional ethical committee clearance was obtained. Women with intact uterus, nonpregnant, and with no past history of cervical neoplasia were selected for the study. Informed written consent of the study participants was obtained.

A detailed sociodemographic and reproductive history was then obtained in a structured questionnaire before subjecting them to screening. In the health centers the primary screening was done by medical officers and women with positive results were referred to the college for further diagnostic evaluation.

A total of 7794 apparently healthy women in the age group of 30-70 years participated in the cervical cancer early detection program between January 2008 and Dec 2011. The present study involved the analysis of 2013 women who tested positive on primary screening by VIA and who further underwent diagnostic evaluation by Pap smear cytology and colposcopy and were subsequently subjected to colposcopy-directed biopsies.

Women underwent screening by VIA. Acetic acid (5%) was applied to the cervix using a cotton swab and VIA findings were reported 1 min after the application as negative or positive. The result of VIA test was recorded positive when there were sharp, distinct, well-defined, dense acetowhite areas with or without raised margins, closer to the squamocolumnar junction in the transformation zone and not far away from the cervical os. The women with negative findings were reassured, counseled, and sent back with an appointment for a next screening date.

In the screening clinic, conventional cytology testing was obtained by scraping the cervical cells with a thin cotton swab by a gynecologist or trained medical

doctor(in health centers) . A smear was prepared by spreading the specimen uniformly across a glass slide, which was immediately fixed in 95% ethyl alcohol contained in a plastic or glass jar and transported to the cytology laboratory.

Cytology results were reported according to the Bethesda system.[10]

All those who were found positive on VIA were subjected to colposcopy directed biopsies. The colposcopic diagnosis and grading was done on Reid index, which assigns scores of 1-8 for the colposcopic appearance of margins, lesion color, vascularity, and iodine staining. [11]

Punch biopsies were obtained from the worst of any abnormal areas under colposcopic guidance. Biopsy specimens obtained were fixed in formalin and were processed and reported using the CIN system at the histopathology laboratory of the Mvj medical college . The study outcome was defined as CIN2 and worse lesions, and this disease threshold was used to calculate sensitivity, specificity, and predictive values of the screening tests.

Data were entered in the institution using a standard computer software . Sensitivity, specificity, and predictive values and their 95% confidence intervals for single and combined tests were calculated using 2 X 2 tables and standard formulae. The data were retrospectively analyzed by selecting 2034 women who were positive for VIA primary screening tests and had undergone cytology smear and colposcopy evaluation and were subsequently subjected to colposcopically directed biopsies.

Results:

Total of 7794 healthy women in the age group of 35-70 years participated in the cervical cancer early detection program. Out of the 7794 women who participated in the cervical cancer screening clinics, 1886 women were found to be acetowhite-positive on primary screening test (VIA). In total 95 cases were excluded from the study due to inconclusive colposcopies and inadequate cytology or biopsy results, leaving 1791 cases to be analyzed.

Colposcopic impression (Table 1) was benign in 850 patients. CIN 1 changes were seen 500, CIN2-3 in 95 cases and frank invasive cancer in 5 cases.

Conventional cytology [Table 2] was found to be normal in 1762 (91.2%) women, ASCUS were seen in 31 (1.6%), low-grade squamous intraepithelial lesion (LGSIL) in 32 (1.6%), HGSIL in 72 (3.7%), and invasive cancer in 32 (1.6%).

Histopathology findings were reported as benign in 1576 (81.6%), atypia or HPV changes in 80 (4.1%), CIN1 in 113 (5.8%), CIN2 in 56 (2.9%), CIN3 in 50 (2.6%), and invasive carcinoma in 56 (2.9%)

Table 1 : Agreement between colposcopic impression and colposcopy directed biopsy

Histopathology	Colposcopy impression					
	Benign	condyloma	CIN 1	CIN2-3	Invasive cancer	Total
Benign	850	60	500	95	5	1510
Atypia /HPV	25	6	30	2	1	64
CIN1	30	5	50	6	0	91
CIN2	15	2	14	12	1	44
CIN3	6	1	5	20	4	36
Invasive cancer	8	2	1	5	30	46
Total	934	76	600	140	41	1791

Table 1sensitivity - 57.14% specificity- 93.45% ,PPV -39.77% ,NPV -96.64%

Table 2 agreement between cytology and colposcopy directed biopsy.

	Cytology						
Histopathology	Benign	HPV	ASCUS	LGSIL	HGSIL	Invasive cancer	Total
Benign	1425	8	35	20	17	5	1510
Atypical or HPV	54	1	4	4	1	0	64
CIN1	77	0	3	8	1	2	91
CIN2	24	0	3	6	10	1	44
CIN3	6	1	4	3	22	0	36
Invasive cancer	10	0	3	0	13	20	46
Total	1596	10	52	41	64	28	1791

TABLE 2 : SENSITIVITY - 49.20% , SPECIFICITY- 97.41% , PPV- 59.04% , NPV- 96.20%

DISCUSSION:

Though cervical cancer can be detected in the earlier treatable stages , the morbidity and mortality due to cervical cancer is not reducing because of the failure of the cervical cancer screening programmes especially in the developing world. In developed countries,Pap smear screening has been successful in reducing the incidence and mortality due to invasive cervical cancer.Organized and frequently repeated cytology screening has resulted in a substantial reduction of cervical cancer burden in developed countries. But in low-resource countries where organized cytology-based cervical cancer screening programs cannot be implemented due to financial, technical, and logistic barriers, low-cost technologies, such as the VIA-based approaches have been successfully tested and proposed to address the need to effectively improve and extend screening services in the country.[2,4], [12,13,14,15,16,3,17,18].With the added advantage of the immediate availability of VIA test result, VIA-positive women can be subjected to further investigative procedures to ensure diagnostic and treatment compliance with a "Single Visit" approach. Diagnostic triage of VIA-positive women by cytology or colposcopy directed biopsy are still not very feasible in low-resource country settings where adequate expertise, facility, and infrastructure are still not available for cytology and histopathology confirmation, outside of the city limits. Also, poor patient compliance for further diagnostic or treatment visits and inadequate patient tracking system creates further barriers in the successful implementation of screening programs.

Hence a "Single Visit" screen and treat strategy that uses VIA and colposcopy alone that eliminates the need for repeated visits due to delays in diagnostic results, will be highly attractive in terms of cost-effectiveness and compliance to treatment, which is crucial to bring down the incidence and mortality due to cervical cancer.

Thus, in the context of adopting VIA-based approach as a primary screening modality in low-resource

settings, we tried to evaluate the performance of colposcopy to estimate the conventional cytology testing to triage VIA-positive women.

The performance and accuracy of colposcopy depends largely on the training, experience, and skills of the colposcopist. Hence, accuracy of colposcopy varies widely among studies in different parts of the world. In a meta-analysis, Mitchell and colleagues report studies that distinguished normal cervix from all other diagnosis, for which the individual estimations of sensitivity of diagnostic colposcopy (87-99%) were high, whereas those of specificity (23-87%) were lower. Similarly, among 8 other studies with fully separated disease categories, for distinguishing normal cervix, atypia, and LGSIL from HGSIL and cancer, the estimates of sensitivity of diagnostic colposcopy ranged from 64% to 99% and the specificity from 30% to 93%. [19]

Also data from Massad and Collins reported that the sensitivity of colposcopy with a threshold of any lesion detected was 89% but fell to 56% when the threshold was raised to a high-grade result. [20]

In the present study, the sensitivity of colposcopy at low thresholds was high (74.5%), but the specificity was lower at 57.5%.

Lower specificity for a diagnostic test would always increase further burden on the health system in terms of unnecessary increased health care cost for treatment of the false positives, which offsets the primary goal of making cancer screening services cost-effective for low-resource settings.

The test characteristics of colposcopy in the current study at high threshold colposcopy impression for detection of CIN2+ histology lesions is almost comparable to that of conventional cytology (sensitivity 57.4%, specificity 99.4%, and NPV 96.2%), wherein cytology smears were tested at a tertiary care institute with internal and external quality control measures adopted in cytology and pathology laboratories.

The above comparable estimates have an important implication in adopting colposcopy to triage VIA-positive women, which obviates the necessity of resource-intensive cytology and also because the performance of cytology is known to be suboptimal outside the centers of excellence or beyond the tertiary care centers in less developed countries. Cytology at lower cutoffs (ASCUS+, LGSIL+), however, shows improved sensitivity in our study but requires laboratory services and skilled cytologists. Also it does not provide immediate results, which entails repeated patient visits for further testing and management and has remained one of the biggest challenges in implementing cytology-based cervical cancer screening programs in the developing country settings.

The present study, however, suffers from the limitation of colposcopy being performed by multiple colposcopists at various levels of expertise, many of them recently trained, presumably in their learning curves during the entire phase of the study.

Although more recent studies suggest that in expert hands colposcopy can be highly accurate, skill levels vary.[6,7,,21,22,23,24,25,9,10,11]

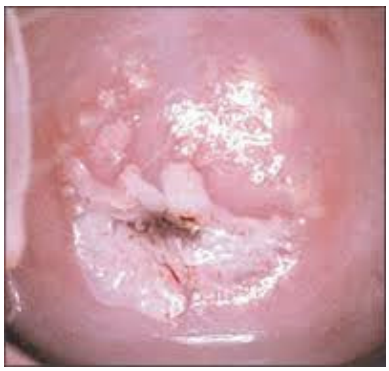
Thus in spite of the above limitations, our findings suggest that colposcopy at lower colposcopy cutoffs shows acceptable sensitivity for a histologic outcome of CIN2+ than cytology, but the specificity of colposcopy is then much lower. Thus colposcopy, which gives immediate results, can be considered as a secondary testing tool to triage women found positive on VIA in settings where cytology and histopathology services are logistically and technically not feasible. The disadvantage of

colposcopy is its lower specificity at low cutoffs and the need for the colposcope and that of a skilled colposcopist.

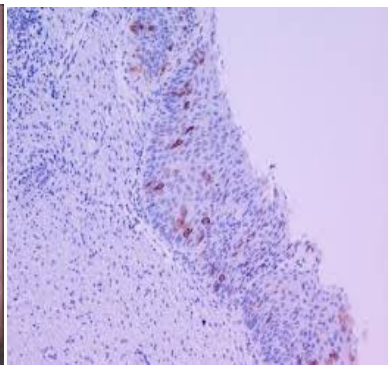
Thus, alternative approaches to the traditional model that reduce the need for extensive cytology and histopathology services would make cervical cancer screening and treatment possible in developing countries.

CONCLUSION:

Colposcopy is a good sensitive test for the detection of CIN and can be considered as a secondary testing tool to triage women found positive on VIA.



Aceto white lesion



HPV changes in same patient

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