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ORIGINAL ARTICLE

Looking Beyond VIA to Improve Cervical Cancer Screening in Low Resource Settings

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Abstract

Background The two prongs for cervical cancer prevention are vaccination for primary prevention and effective screening for preinvasive and early invasive disease. Until human papilloma virus DNA testing can be provided in low resource settings, screening with VIA is the most feasible option. Various innovative methods have been used to improve the diagnostic accuracy of visual inspection with acetic acid (VIA). This study explores one such option.

Method We modified VIA (VIA-Md) by using a magnifying lens mounted with battery operated light emitting devices (LEDs) to study the acetowhite areas on the cervix. The peak wavelength of the light from the LEDs was in the bluish white range. The results of VIA and VIA-Md were compared using colposcopy directed biopsy as the reference standard.

Result The study was conducted in 273 eligible women. The sensitivity of VIA and VIA-Md for detecting CIN2 + lesions were 57.1% and 100% respectively. The specificity of VIA and VIA-Md were 99.2% and 89.5%; and *p* values using the colposcopy directed biopsy as the reference standard were 0.000 and 0.018 respectively. However, VIA-Md was also effective in identifying 21 out of the total 32 cases of chronic cervicitis identified by colposcopy directed biopsy.

Conclusion VIA-Md appears to be a highly sensitive test for detection of CIN2 + lesions. However, because of concerns regarding lower specificity, VIA-Md can be used simultaneously with VIA as an effective tool for triaging women who need to be kept under close surveillance or who might benefit from local ablative therapy.

Keywords Cervical cancer · VIA · VIA-Modified · Cervical cancer screening · Bluish-white light

Abbreviations

VIA	Visual inspection with acetic acid
VIAM	Visual inspection with acetic acid under low grade magnification
VIA-Md	Visual inspection with acetic acid – modified by adding bluish-white light and low grade magnification
LED	Light emitting device
CIN2 +	Cervical intraepithelial neoplasia grade 2 or 3
MRCI	Modified reid's colposcopic index
HPE	Histopathological examination
HSIL	High grade squamous intraepithelial lesion
LSIL	Low grade squamous intraepithelial lesion
ASC-H	Atypical squamous cells – high grade

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Introduction

According to global cancer statistics 2020, cervical cancer is the fourth leading cause of cancer-related deaths in women worldwide; 90% of cases are contributed by countries with a low human development index [1]. In India, cervical cancer is the second most common cancer among women, next only to breast cancer. Since screening for high-risk human papillomavirus (HPV) DNA and cytological testing for malignant

or premalignant cells have been found to be resource-intensive, visual inspection of cervix after applying 3–5% acetic acid (VIA) has been proposed for mass screening of cervical cancer [2]. Although VIA is simple, cost-effective, and easy to perform, its major limitation is subjectivity and poor reproducibility. This is reflected in the low sensitivity of the test in a community setting [3].

In order to improve the sensitivity of VIA, portable colposcopes have been investigated but the cost of these devices is a major limiting factor in the wide-scale provision of such instruments in the field setting [4, 5]. Therefore, there is a need to develop a simple cost-effective method, accessible even in remote peripheral areas, which can improve the performance of VIA in cervical cancer screening. The use of a simple handheld magnifying lens or a loupe can enhance magnification by two-fold to five-fold. However, low power magnification alone has not been found to be effective in improving the diagnostic accuracy of VIA [6]. Previous studies have shown that the use of blue-white light obtained from chemiluminescence using speculite along with magnification can enhance the sensitivity of VIA. This procedure is called 'speculoscopy' [7]. Further, it has been investigated in conjunction with conventional cytology to improve the sensitivity of conventional cytology for detecting premalignant and early malignant lesions of cervix [8, 9] However, since speculite uses chemiluminescence and can only be used once, it is not cost-effective for resource-poor settings.

Based on the principle of speculoscopy, we designed a study to evaluate the efficacy of Visual Inspection with Acetic acid (VIA), modifying it by adding bluish-white light from light-emitting devices (LEDs) and low magnification (VIA-Md) for detection of high-grade cervical intraepithelial neoplasia (CIN 2,3) and early invasive lesions of cervix, i.e., CIN2 + lesions. Our hypothesis is that modification of VIA by adding bluish-white light from LEDs and low-level magnification to VIA improves the resolution of the image, thus improving the diagnostic accuracy of the test.

Materials and Methods

We designed a cross-sectional study to compare the diagnostic accuracy of VIA and VIA-Md in the detection of preinvasive and early invasive lesions of the cervix. Colposcopy and directed biopsy were used as the reference standard for comparison. The study was conducted in the outpatient clinic of the Obstetrics and Gynecology department in a tertiary care hospital.

The study was conducted in accordance with the Declaration of Helsinki. Research and ethical approval were granted by the institutional review board. Informed consent was taken from all participants.

A sample size of 273 was calculated using 79% diagnostic accuracy of VIAM computed in another study and using 95% confidence interval and 10% permissible errors. Women aged 21–65 years, sexually active for at least 3 years, were included in the study in a consecutive manner after obtaining informed consent. Patients with a history of total hysterectomy, gynecological cancer, frank cervical growth, type III squamocolumnar junction, active vaginal bleeding, acute cervical infection, and current pregnancy were excluded.

After taking a detailed demographic, medical, and obstetric history, all patients were subjected to a general and local examination by a resident doctor specifically trained for this project using the IARC Colposcopy Manual [10]

The following procedures were performed in succession on each patient:

First, the vagina and the cervix were inspected for any visible lesions. Second, a conventional Pap smear was obtained from the uterine cervix using an Ayre spatula. Third, a cotton wool swab soaked in 5% freshly prepared acetic acid solution was applied to the cervix. The area was then inspected after one minute for acetowhite lesions which were marked in a diagrammatic representation of cervix. The cervix was then inspected using a battery-operated handheld lens fitted with small bluish-white light-emitting devices (LEDs) at the periphery (Fig. 1).

Any additional findings were marked in a different color on the same diagram. Next, a colposcopy examination was performed in the usual manner. Findings of colposcopy were recorded, and biopsies were performed for any suspicious areas. Histopathological examination and cytological testing were conducted by the Department of Pathology within the institute and the test samples were graded using the Bethesda system. Statistical analysis was done using the latest SPSS Version. Descriptive statistics were obtained for all study variables. All categorical variables were compared using Chi-square and Fisher's exact test and continuous variables using Student's t-test. For all statistical analyses, $p < 0.05$ was considered significant.

Fig. 1 Biconvex lens mounted with battery operated light emitting devices at the periphery

Specifications of the lens

We used a biconvex lens of 67 mm diameter with a power of 4.5 diopters giving a magnification of approximately 200%. The peak wavelength of the light emitted by the five LEDs was 449.50 nm (Fig. 2.) The LEDs were powered by three double AA batteries of 1.5 Amperes each. The lens was purchased locally from a medical equipment vendor for INR 200 (approximately USD 3) and was found to be easily available in stores selling medical equipment.

Results

Three hundred women were enrolled for the study, 27 had to be excluded because of an unsatisfactory examination due to acute infection, significant bleeding on touch, or a type III squamocolumnar junction. These women were managed appropriately in the clinic. The findings of 273 women were analyzed for the purpose of this study.

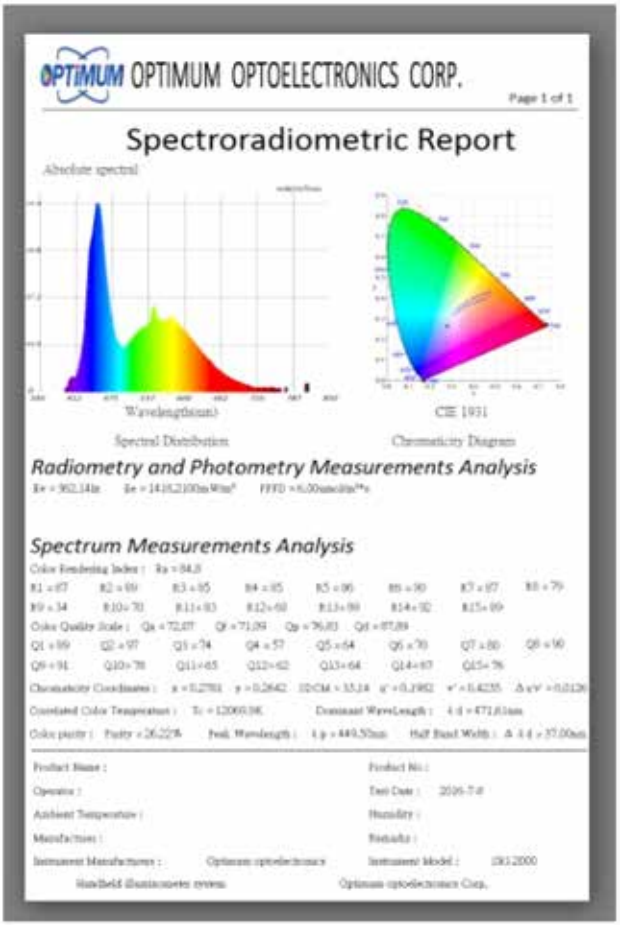

Fig. 2 Spectrum of the light emitted by the light emitting devices mounted on the lens (*Courtesy*: Dr. Aparna, Senior Scientist, Central Scientific Instrument Organization, Chandigarh)

The mean age of the women was 38.05 + − 9.41 years, 86.1% ($n = 235$) belonged to urban areas while 13.9% ($n = 38$) belonged to rural areas; 69.6% ($n = 190$) had one or two children, while 30.4% had 3 or more children. We could not find any significant correlation between the presence of a lesion and any of the demographic factors in this study.

The most common complaint was that of vaginal discharge present in 26.4% ($n = 72$) women, while 10.2% ($n = 28$) complained of post-coital or post-menopausal bleeding. Colposcopy with directed biopsy was used as the reference standard and Modified Reid's Colposcopic Index (MRCI) was calculated for all patients [10]. The details of MRCI scores have been provided in Table 1. Punch biopsy was taken for women with a positive score. Among the 53 women for whom biopsies were taken, four biopsies were reported as Squamous Cell Carcinoma, while 10 were reported as High grade squamous intraepithelial lesion (HSIL) on histopathological examination (HPE). These patients were managed appropriately. Hence 5.1% ($n = 14$) women in this cohort had CIN2 + lesions, chronic cervicitis was reported in biopsy of 11.7% ($n = 32$) women while the biopsy showed normal tissue findings in 2.6% ($n = 7$) cases. The histopathology results showed a highly significant correlation with the MRCI scoring, $p < 0.001$. The results of the various tests and examinations are as follows:

1. Direct visual inspection of cervix

On examination, cervix looked normal in 86.44% ($n = 236$) women. Leukoplakia ($n = 1$), cervical lesion ($n = 1$), cervical polyp (n = 6) and hypertrophy with chronic cervicitis ($n = 29$) were the abnormalities noted in remaining 14.36%. However, 9 of the 14 preinvasive or invasive lesions (64.3%) were detected in patients with apparently normal-looking cervix. On analysis, direct visual examination of cervix showed poor correlation with the biopsy report, p-value of 0.264.

2. Pap smear

Only eight of the 14 biopsy-confirmed CIN2 + lesions could be correctly identified with conventional cytology.

Table 1 Results of colposcopy

MRCI score (expected histology report)	No. of patients
Score 0 (Normal cervix)	220
Score 0–2(Likely to be CIN I)	28
Score 3–4(Overlapping lesions – likely to be CIN 1 or CIN 2)	13
Score 5–8 (Likely to be CIN 2 or CIN 3)	12

Three of the eight low-grade squamous intraepithelial lesions (LSIL) detected by cytology showed chronic cervicitis on HPE while in 5 cases, colposcopy directed biopsy specimens were reported as normal. Among the 13 high-grade lesions diagnosed as HSIL ($n=9$) or ASC-H ($n=4$) on cytology, HPE confirmed CIN2 + lesions in 8 patients and chronic cervicitis in 5 patients. While there was a high likelihood of biopsy-confirmed CIN2 + lesion if cytology was suggestive of a high-grade lesion (LR = 20.78), the sensitivity of cytology for detection of CIN2 + lesions was found to be only 57%.

3. Visual inspection using acetic acid

There were 10 VIA-positive cases out of which HSIL was detected in 5 cases and invasive cancer in 3 cases. However, 6 patients reported as VIA negative were subsequently detected to have positive colposcopy findings and were reported to have CIN2 + lesions in HPE of the biopsy. Although analysis showed a high positive predictive value and a high likelihood ratio of 16.44 for the presence of disease when VIA was positive, the sensitivity of VIA to detect preinvasive or early invasive lesions was found to be 57.1%. VIA findings significantly correlated with colposcopy-directed biopsy, p-value < 0.001.

4. Visual inspection using acetic acid–modified (VIA-Md)

On VIA-Md, 15% ($n=41$) of subjects were reported as positive. All 14 patients who were diagnosed to have premalignant or malignant lesions on biopsy were VIA-Md positive, giving a sensitivity of 100% and p-value of 0.019. However, VIA-Md was also positive in women with chronic cervicitis ($n=21$) and women with normal cervix ($n=6$). Hence, although sensitivity for high-grade lesions and invasive cancer was 100%, specificity was poor; the likelihood ratio for CIN2 + lesions was low (LR = 8.56) in comparison to VIA (LR = 16.44).

The correlation of various screening methods and the HPE reports has been shown in Table 2. Comparison of sensitivity, specificity, and predictive values for detection of CIN2 + lesions by various methods has been shown in Table 3. The reference standard for comparison is colposcopy-directed biopsy.

Table 2 Correlation of various screening methods and histopathology report

	Biopsy positive	Biopsy negative/colposcopy normal	p value
Direct VI suspicious	5	26	$p=0.264$
Direct VI normal	9	233	
Pap smear positive	8	13	$p<0.001$
Pap smear negative	6	246	
VIA positive	8	2	$p<0.001$
VIA negative	6	257	
VIA-Md positive	14	27	$p<0.016$
VIA-Md negative	0	232	

Table 3 Comparison of sensitivity, specificity, and predictive values for detection of CIN2 + lesions by conventional Pap, VIA and VIAM

High grade lesion	Sensitivity %	Specificity %	PPV %	NPV %
Pap smear	57.1	94.9	38	97.6
VIA	57.1	99.2	80	97.7
VIA-Md	100	89.5	34.1	100

Discussion

In 2020, WHO launched a global strategy for cervical cancer elimination which is the first-ever global commitment towards this goal. It includes achieving 70% coverage of screening with high-performance tests equivalent to or better than HPV testing [11]. However, at present, HPV DNA testing does not appear to be feasible in low- and middle-income countries. Accordingly, countries like India and Bangladesh, with a high burden of disease, are still focusing on programmatic interventions that use VIA for the detection of preinvasive and early invasive cervical cancer [12]

Although the current recommendation is for regular screening at five-year intervals, there are programmatic difficulties in implementing the protocol [2, 13] The fact that currently, less than 2% of eligible women in India have ever undergone screening for cervical cancer underscores the need for a highly sensitive screening test [14]

Previous attempts at increasing the sensitivity of VIA by using 2-3 X magnification have not been found to be significantly better than VIA [6, 15, 16]. Therefore, the need for better visualization during VIA has prompted researchers to innovate and to look out for strategies to improve the sensitivity of VIA [4, 5]. However, these innovations can only be effective if they can be provided at a large scale in a cost-effective manner.

In this hospital-based study, we were able to achieve 100% sensitivity for detecting CIN2 + lesions by using a simple magnifying lens in the presence of bluish-white light. We believe that the low-level magnification coupled with bluish-white light was more effective in highlighting the acetowhite areas in comparison with simple low-level magnification which was used in previous studies. This phenomenon of selective absorption and reflection of various wavelengths of visible light by different tissues has

been observed by other researchers while using speculoscope as well as in a study focused on early detection of oral cancer [17].

One major concern with the use of magnification with VIA is a decrease in specificity for CIN2 + lesions. In our study, the specificity of VIA-Md for CIN2 + lesions was found to be 89.5% compared to a specificity of 99.2% with VIA. However, out of the total 27 false-positive cases, 21 cases also showed some positive findings on colposcopy and the directed biopsy revealed chronic cervicitis in those cases. Further, 6 of these women with chronic cervicitis on biopsy also showed positive findings on pap smear ranging from LSIL to Atypical Squamous Cells – High Grade (ASC-H). Chronic cervicitis has been linked to persistent HPV infection, cytological abnormalities, and increased predisposition to develop precancerous and cancerous lesions [18]. Therefore, we believe that it is important to identify chronic cervicitis so that the affected woman can be appropriately managed and advised close follow up. Thus, out of the 41 cases in which VIA-Md was positive, 35 cases had a significant lesion, and 6 cases were false positive.

An important clinical application of VIA-Md can be using it as a simultaneous test with VIA, in which case women testing positive for both VIA and VIA-Md can be treated or referred for further management, while those testing positive only for VIA-Md can be kept under surveillance.

Another important benefit of VIA-Md is a shorter learning curve, better pattern recognition, and increased confidence in the test provider because of a better visual experience. This contrasts with VIA because the interpretation of VIA can be difficult for healthcare professionals with limited experience [19] Thus, VIA-Md can enhance the characterization of findings as well as the reproducibility of the test.

One of the major limitations of this study was that we did not test for the reproducibility of results for VIA-Md. A different study design in which two different examiners record their findings separately for comparison later would be required to check for this feature. Also, in this study, VIA-Md was performed using a specific spectrum of bluish-white light with a peak wavelength of 449.5 nm. There is a need to study whether the enhanced visualization occurs with a slightly different spectrum of bluish-white light and will give similar results. The role of adequate light intensity may also need to be characterized. Further, this study was conducted in controlled conditions by a well-trained physician, the results may vary in the hands of less-trained personnel.

However, there are numerous strengths of this study. Firstly, the single observer design ensured uniformity of test characteristics in this study. Secondly, this study provided us with an opportunity to compare three different modalities of cervical cancer screening against a reference standard. Thirdly, since all procedures were done in the same sitting, the design of the study was patient-friendly.

Conclusion

VIA-Md appears to be a highly sensitive test for the detection of CIN2 + lesions. Thus, it can enhance the effectiveness of VIA-dependent cervical cancer screening programs in resource-poor settings. However, because of concerns regarding lower specificity, VIA-Md can also be used simultaneously with VIA as an effective tool for triaging women who need to be kept under close surveillance or who might benefit from local ablative therapy. Improved visualization of aceto-white areas can also help in enhancing the characterization of lesions by the test provider.

Implications for Practice

Enhanced performance of modified VIA (VIA-Md) for detecting precancerous lesions of the cervix and identifying women who need a close follow-up can boost VIA-based cervical cancer screening programs in low-resource settings.

Further Research

We have designed a study to test the diagnostic accuracy of VIA-Md in a community setting in the hands of trained nurses in peripheral health centers using a ‘see and treat’ approach for cervical cancer screening [2, 20].

Acknowledgements The manuscript has not been submitted to more than one journal for simultaneous consideration. The submitted work is original and has not been published elsewhere in any form or language. Results are presented clearly, honestly, and without fabrication, falsification or inappropriate data manipulation.

Author Contributions AD: Design of study; acquisition, analysis, and interpretation of the data; drafting the manuscript. AS: Refining the methodology, revising the manuscript critically for important intellectual content. BG: Innovative use of the instrument; development of the concept and design of study; analysis and interpretation of the data, drafting the manuscript. SD: Acquisition, analyses and interpretation of the data.

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Declarations

Conflict of Interest None declared.

Ethical Approval The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the institutional review board. Informed consent was taken from all participants. The research project was approved by the Institutional research and ethics committee.

Informed Consent An informed consent was taken from the participants for publication of the findings of the study while taking care to protect their privacy and maintain their confidentiality.

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