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COMPARING THE RESULTS OF VIA, VILI, PAP'S SMEAR FOR SCREENING OF CANCER CERVIX WITH HISTOPATHOLOGY AS GOLD STANDARD.

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ABSTRACT

Objective: The current study was planned to compare the diagnostic accuracy of visual inspection of cervix after application of 3% acetic acid (VIA), visual inspection of cervix after application of Lugol's Iodine (VILI) and Pap smear with colposcopy guided biopsy as gold standard to detect cervical neoplasia. **Material and method:** In this prospective study, 120 women attending obstetrics and gynecology department of a tertiary care teaching hospital between November 2021 to November 2022 were included. Women with active bleeding, pelvic infection and already diagnosed with cervical neoplasia were excluded. A Papanicolaou smear and visual inspection of the cervix with 3% acetic acid and Lugol's Iodine was done. All patients who tested positive on screening then underwent a colposcopy examination followed by guided biopsy from the abnormal area. The statistical test used was the chi-square test to compare the proportions. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated for VIA, VILI, Pap's smear, and Colposcopy with histopathology as the gold standard. **Results:** Fifty-eight patients (48%) were diagnosed positively by the gold standard investigation histopathology examination (HPE). Most common diagnosis was CIN I (N=46; 79%) followed by CIN II (N=7). The positive diagnosis by all 4 screening tests were 55%, 60%, 54% and 61% by VIA, VILI, Pap's smear, and colposcopy respectively. Diagnostic accuracy of VIA, VILI, Pap's smear, and colposcopy in present study was 88.3%, 84.9%, 92.5% and 86.67% respectively. **Conclusion:** All four tests studied including VIA, VILI, Pap's smear, and Colposcopy had significant diagnostic accuracy as a screening test for cervical neoplasia. Pap's smear had maximum diagnostic accuracy of 92.5%.

KEYWORDS

Cervical cancer, screening, colposcopy, visual inspection, acetic acid, Lugol's Iodine, Pap's smear, diagnostic accuracy

INTRODUCTION

Cervical cancer is the commonest malignancy in Indian women accounting for almost 30-40% of all cancers in this population (1). Early detection by screening programs have resulted in significant reduction in the burden of cervical cancer in developed countries. World Health Organization (WHO) recommends once in a lifetime screening of all women at the age of 40 years (2). A once-in-a-lifetime Papanicolaou (Pap) smear with follow-up colposcopy and treatment results in a 19% reduction in cervical cancer (3). However, a cytology-based screening program requires considerable technical, financial, and human resources, and feasibility is doubtful in resource-limited countries like India. Visual inspection-based screening methods are an alternative for early detection of cervical neoplasia (4). The current study was planned to compare the diagnostic accuracy of visual inspection of cervix after application of 4% acetic acid (VIA), visual inspection of cervix after application of Lugol's Iodine (VILI) and Pap smear with colposcopy guided biopsy as gold standard to detect cervical neoplasia.

MATERIAL AND METHOD

In this prospective study, 120 women attending Obstetrics and Gynecology department of a tertiary care teaching hospital between November 2021 to November 2022 were included. Women with active bleeding, pelvic infection and already diagnosed with cervical neoplasia were excluded. The study was approved by the institute ethics committee. After obtaining the informed consent of the patients, detailed demographic information and clinical history were obtained on a pre-defined structured proforma.

After explaining the procedure, all these patients underwent speculum examination by Cusco's self-retaining speculum and Pap smear was taken from the transformation zone of cervix. Then 3% acetic acid solution was applied for 30-60 seconds and acetowhite area was looked for. If acetowhite area was found, then patient was labelled as VIA positive. We further proceeded by applying Lugol's iodine. If any area showed no uptake of iodine, then that area was labelled as VILI positive. This was followed by colposcopic examination of cervix and abnormal area was defined as abnormal vasculature in the green filter, acetowhite area in the transformation zone, negative iodine uptake or any growth from the cervix. Wedge biopsy was taken from the abnormal area based on VIA positive, VILI positive, Pap smears positive or abnormal colposcopy results. Slides were examined in the Pathology department. Findings of Pap smear were reported as per Bethesda system. Pap smear finding was graded as: ASC-US, ASC-H, AGL/AIS, LSIL, HSIL and anything suggestive of LSIL or above was defined as Pap smear positive.

Sample size (N=120) was calculated at 95% confidence interval to verify an expected 20% proportion of women having CIN among women positive for visual inspection by acetic acid as reported by a previous study and 20% relative allowable error. Results were then compiled and analyzed. IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) was used for the analysis. Chi-square test was used to compare proportions. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated for VIA, VILI, Pap smear and Colposcopy, with histopathology as the gold standard. A receiver operating characteristics (ROC) curve was also derived.

RESULTS

Of the 120 women screened for the cervical lesions, 40% (N=48) were from the age group of 36-40 year. The mean age of the cohort was 35 years (SD=4.5) ranging from 26 to 44 years. The mean age of menarche was 12.8 years (SD=1.0). Socio-demographic details of the cohort are as shown in table 1.

Table 1: Socio-demographic characteristics

Parameter	N=120
Age (years), Mean (SD)	35 (4.5)
Age at menarche (years), Mean (SD)	12.8 (1)
Age at marriage (years), Mean (SD)	18.5 (2.1)
Duration of marriage (years), Mean (SD)	16.4 (5.2)
Rural, number (%)	78 (65%)
Literate, number (%)	76 (63%)
Socio-economic class, number (%) • Lower middle • Upper lower • Lower	24 (20) 33 (27) 63 (53)

Sixty-six (55%) patients had a history of addiction to some substance abuse and tobacco chewing was the most common addiction (20%). Leucorrhea (39%) and lower abdominal pain (38%) were the commonly presenting complaints. The sensitivity, specificity, PPV, NPV, likelihood ratio and diagnostic accuracy for all these tests with

histopathology examination (HPE) as gold standard diagnostic investigation have been displayed in table 2. Out of these tests, Pap smear had maximum diagnostic accuracy (92.5%). The ROC curve was plotted between the sensitivity and 1-specificity and was compared between 4 different tests. Area under curve was maximum for Pap smear (0.927; 95 % confidence interval 0.873-0.980) and all 4 tests have significant area under curve against HPE as gold standard investigation suggesting significant diagnostic accuracy (all p value<0.05) (figure 1).

Table 2: Diagnostic parameters of various tests with HPE as gold standard investigation

Test	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Likelihood ratio + (95% CI)	Likelihood ratio – (95% CI)	Diagnostic accuracy
VIA	94.8% (89.1 – 100.5)	82.2% (72.7 – 91.7)	83.3% (74.3 – 92.3)	94.4 % (88.3 – 100.5)	5.34 (3.11 – 9.16)	0.06 (0.02 – 0.19)	88.3 %
VILI	96.5 % (88 – 99.5)	74.2 % (61.5 – 84.5)	77.5 % (69.3 – 84.1)	95.9 % (85.6 – 98.9)	3.74 (2.45 – 5.72)	0.05 (0.01 – 0.18)	84.9 %
PAP smear	98.2 % (94.9 – 101.6)	87 % (78.7 – 95.4)	87.6 % (79.7 – 95.6)	98.1 % (94.6 – 101.7)	7.61 (3.98 – 14.55)	0.01 (0.002 – 0.138)	92.5 %
Colposcopy	100 %	74.1 % (63.3 – 85.1)	78.3 % (68.9 – 87.7)	100 %	3.87 (2.54 – 5.90)	0	86.7 %

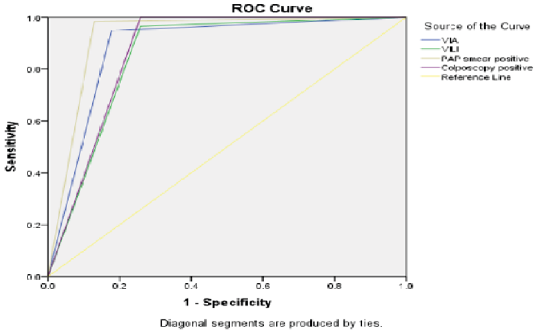

Figure 1: Receiver operating characteristics (ROC) curve comparing 4 different tests with HPE as gold standard investigations.

DISCUSSION

The commonest age group observed in the current study was 36-40 years (40%) followed by 25-30 years group (25%). Age group of 41–45 years had only 11% patients. In a study done by Goel et al, maximum patients belonged to the age group of 30-34 years (5). Another study by Divya Hegde et al included 56.6% patients from the age group of 41-50 years (6). A relative shift to lower age group was observed in our study which may be due to prevalence of marriage at an early age in the population studied, which leads to early intercourse and thus early exposure to HPV which leads to symptoms like vaginal discharge. Leucorrhea (39%) and lower abdominal pain (38%) were found to be the most common presenting complaints. This is in consonance with the previous studies (7,8).

The sensitivity of VIA was 94.8% (95% confidence interval 89.1-100.5) and specificity was 82.2% (95% confidence interval 72.7-91.7). In another study by Saleh in 2016 similar results of VIA examination were reported with sensitivity of 91.30%, and specificity of 85.33% (9). In the current study, the positive predictive value of VIA was reported as 83.3%, while negative predictive value was 94.4%. Saleh et al reported positive predictive value of 40.11% and negative predictive value of 98.05% (9). Another study by Saleh et al in 2014 reported VIA had a sensitivity of 90%, specificity of 37%, and positive predictive value of 52% and negative predictive value of 81% (10). The difference in specificity and positive predictive value from the current study may be noted because of observer variance and using 3% acetic acid as compared to 5% acetic acid being used in previous studies. Similar sensitivity and specificity were reported by another Indian study (11). Low specificity is the limitation of VIA that inevitably results in referral and/or treatment of false positive lesions. Therefore, it is essential to find methods to improve the specificity of VIA. Magnification did not improve the specificity of VIA in 2 South African cross-sectional studies (12). Standardized training, uniform and reproducible criteria for VIA test positivity and development of quality control procedures may further contribute to improvements in test characteristics of VIA. The inability to detect endocervical disease is another potential limitation of VIA. Many meta-analyses have reported the accuracy of VIA. A meta-analysis published a review on the performance of VIA, pooling 7 studies. The authors report a sensitivity of 84% (range, 66% to 96%) and specificity of 82% (range, 64% to 98%) (13). A more recent meta-analysis pooled 11 studies performed in Africa and India. The authors reported a sensitivity of 79% (range, 73% to 85%), specificity of 85% (range, 81% to 89%) and positive predictive value (PPV) of 12% for lesions greater than or equal to CIN2 (14).

VILI provides another useful low-technology method for cervical cancer screening in developing countries. In the current study, the sensitivity of VILI was 96.5 % (95% confidence interval 88-99.5), specificity was 74.2 % (95% confidence interval 61.5-84.5), positive predictive value of 77.5%, negative predictive value of 95.9% and diagnostic accuracy was 84.9%. Another Indian study reported the sensitivity of VILI as 87.2% (95% confidence interval 80.6-92) and specificity 84.7% (95% confidence interval 83.6-85.8), positive predictive value of 16.6%, and negative predictive value of 99.5% (11).

In the current study, the sensitivity of Pap smear was 98.2% (95% confidence interval 94.9-101.6) and specificity was 87% (95% confidence interval 78.7-95.4). The positive predictive value of Pap smear was 87.6%, negative predictive value was 98.1% and diagnostic accuracy was 92.5%. Out of these tests, in our study, Pap's smear proved to have maximum sensitivity as well as specificity thus leading to maximum diagnostic accuracy (92.5%). Another recent study by Christe and colleagues reported Pap smears with specificity of 96%, diagnostic accuracy of 92%, sensitivity of 25%, and missed two cases of cervical cancer and four cases of HSIL (15). Another Indian study reported similar sensitivity of Pap's smear as 83% and specificity of 98% (6).

Colposcopy is a valid tool for the diagnosis of early cervical neoplasia. In our study sensitivity of colposcopy was found to be 100% but its specificity was 74.1%, diagnostic accuracy was 86.67% Another validation study reported similar accuracy of 89% (16). Colposcopy performed better in differentiation of high grade from low grade disease than in differentiation of low-grade disease from normal cervix in that study (16).

Diagnostic accuracy of VIA, VILI, Pap's smear, and colposcopy in present study is 88.3%, 84.9%, 92.5% and 86.67% respectively. Thus, Pap's smear is found to be the most accurate test to detect cervix cancer in its early stage in our study. Ghosh and colleagues found visual tests VIA and VILI to be more accurate than Pap's smear and told that visual inspection methods can replace pap's smear for screening of cancer cervix (17).

Another study from India by Qureshi and colleagues reported that Pap smear had higher specificity than VIA and VILI, but sensitivity of both VIA and VILI was higher than that of pap's smear (18). VIA may have lesser diagnostic accuracy than Pap's smear because not all epithelium that turns acetowhite is abnormal. Any cell with enlarged nucleus or cells traumatized by infection may exhibit varying degrees of acetowhiteness. Thus, it may lead to overestimation of the disease burden and decrease diagnostic accuracy of the test. In the present study diagnostic accuracy of colposcopy is found lesser than that of Pap's smear which may be due to the observer variation. Colposcopy individually may have low specificity but if combined with Pap's smear these tests can complement each other and give better results. The area under curve (ROC curve) was maximum for Pap's smear and all 4 tests have significant area under curve against HPE as gold standard investigation suggesting significant diagnostic accuracy of all these tests for screening of cancer cervix.

There are a couple of limitations to this study. Firstly, the sample size was limited and so a large multi-centre study is recommended to support the findings. Secondly, all four tests were done in the same sitting. Colposcopy was done after taking Pap's smear due to which

cells of transformation zone might be exfoliated giving false results. HPV DNA testing was not included in the study which is another method for screening of cancer cervix.

CONCLUSION:

All four tests studied including VIA, VILI, Pap's smear, and Colposcopy had significant diagnostic accuracy as a screening test for cervical neoplasia. Pap's smear had maximum diagnostic accuracy of 92.5%.

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