ORIGINAL ARTICLE

Comparison of Sensitivity and Specificity of Papanicolaou Test, Visual Inspection of Cervix with Acetic Acid (VIA) and Colposcopy in Cervical Cancer Screening in Patients with Secondary Immunodeficiency

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Abstract

Purpose Cervical cancer is one of the most common problems in public health, especially in developing countries, which is identifiable by screening programs. This study aimed to compare the sensitivity and specificity of Papanicolaou test, visual inspection of cervix with acetic acid and colposcopy in immunodeficient patients.

Methods This examination on the test study was conducted on 135 immunodeficient patients who were referred to Afzalipour Hospital, Kerman, for cervical cancer screening from 2017 to 2018. In the first visit of all the patients, 3 separate tests of Papanicolaou test, VIA and colposcopy were simultaneously performed, and the results were recorded. To analyze the data, descriptive and analytical methods and SPSS software version 20 were used.

Results Most of the cases were between 20 and 40 years old. The most frequency of immunodeficiency was noted among patients with AIDS (19.3%). According to the results of the colposcopy, VIA, Papanicolaou test and biopsy, 77%, 77.8%, 73.3% and 77% of the results were normal, respectively. Most patients were ASCUS in Papanicolaou test, and twenty-one of them were cervical intraepithelial neoplasia 1 (15.6%). Sensitivity, specificity, positive and negative predictive values of colposcopy were more than those of VIA and Papanicolaou test (74.1%, 92.3%, 74.1% and 92.3%, respectively).

Conclusion The results of the study showed that colposcopy is an appropriate method for cervical cancer screening in immunodeficient patients. Accordingly, at times when it is not possible to screen with other methods such as Papanicolaou test, this method may be used in preliminary evaluation.

Keywords Sensitivity and specificity · Papanicolaou test · Visual inspection of cervix with acetic acid (VIA) · Colposcopy · Uterine cervical neoplasms

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Introduction

Cervical cancer is among the most common causes of mortality in developing countries. Almost 500,000 women around the world have cervical cancer, which causes 270,000 of them die each year. According to the results of studies, 80% of deaths caused by cervical cancer and 88% of deaths caused by cancer occur in developing countries [1]. Therefore, early diagnosis of cervical cancer can reduce the related mortality rate [2].

Most countries having organized screening programs could successfully control such cancer [3, 4] that is because screening is highly important in early diagnosis of cervical cancer. Considering that precancerous conditions of cervical cancer are long, if patients are treated in precancerous

neoplasia stage, they will have a survival rate of nearly 100% [5–7].

Papanicolaou test is a simple cytological test for diagnosing cervical cancer [8], which has been done as a screening test for pre-malignancies and intraepithelial cervical cancer in women over 18 years old for more than 50 years, and the result of such test is to distinguish cases of cancer, to prevent progress of disease and to reduce death rate [9]. Nevertheless, due to 50% sensitivity of Papanicolaou test [10], other diagnostic methods including VIA and colposcopy are also used.

After visual inspection of cervix with 5% acetic acid solution, if there is an intraepithelial lesion, that point turns into white; this can be also seen with naked eye, which indicates the positive result of the test [11]. This method does not need high technology, it gets immediate result in 2 min, it can be done by healthcare providers, it costs low, it can be done at the same time with patient examination, it needs no professional medical equipment, and it needs no secondary person for interpreting the test result. Preliminary studies showed that the sensitivity of VIA is similar to or even higher than that of Papanicolaou test, but the low specificity of such method has limited it [12].

The other diagnostic method is colposcopy, which is used to have an extensive complete vision of the internal areas of women's genital organ. Most of the feeble malignant lesions in such areas have definable features that can be diagnosed by examining the patient [13].

Cervical lesions are more aggressive in patients with immunodeficiency; moreover, their process in such patients may differ from other patients. Accordingly, other more effective methods should be used for cervical screening in this group of women. Presently, on the basis of guideline ASCCP 2012, Papanicolaou test is taken every 3 years in women without symptoms and with healthy immune systems. In women over 30 years old, a combination of Papanicolaou test and HPV could be used and screening intervals may be increased to 5 years. However, the same guideline mentions that such interval and method may not effective enough in patients with deficient immune system [14].

So, the objective of the present research is to compare the sensitivity and specificity of Papanicolaou test, VIA and colposcopy, in cervical cancer screening in patients with secondary immunodeficiency.

Materials and Methods

Study Design and Sample Collection

This was a review of the test study. A sample of 135 patients with immunodeficiency who have referred to Afzalipour Hospital, Kerman, Iran, from 2017 to 2018 were participated in study. The criteria for the study included being married, no pregnancy, and aging over 21 or within 3 years of starting sexual activity, without previous complete hysterectomy or previous history of cervical lesions treatment. A patient with secondary immunodeficiency refers to kidney transplant recipients, HIV patients (who have not entered AIDS phase), patients who are treated with drugs controlling immune system such as cyclosporine, tacrolimus, sirolimus, azathioprine, cyclophosphamide, thalidomide and etanercept for more than 2 months, or patients who have recently taken Corticosteroids with a dose of 15 mg/day for at least 3 months, and patients with a cancer except cervical cancer who have underwent chemotherapy for more than 2 months.

Using the following formula, the sample size was taken 39, which was increased to 135 in order for better results.

$$n = \frac{z^2 p(1-p)}{d^2}$$

Ethical Considerations

After receiving ethical code from Kerman University of Medical Science (Code: IR.KMU.AH.REC.1397.045), informed consent was taken from all the patients.

Data Collection Procedures

In all patients' first visit to the hospital, three separate tests of Papanicolaou test, VIA and colposcopy were simultaneously taken, and the results were recorded.

Papanicolaou test

As for Papanicolaou test, the method was so that the handle of cytobrush was cut short, and then, it was dropped directly into the retaining fluid and sent to the laboratory. After shaking the whole retaining fluid for 30 s, it was poured into the tube. In order to separate debris and mocus, 4 ml of cleaning solution was added into the tube. After centrifuging with a speed of 1200 g for 10 min, 0.5 ml of cellular base solution was added to the sediment in order to cause decapitation and cohesion appropriate for controllable cell number on the slide. After shaking and mixing, 50 μl of the homogeneous suspension was poured on the slide by using a sampler so as to dry at room temperature. It was colored using Papanicolaou method and was given to the pathologist. The result was classified according to Bethesda 2001 system. The cases above ASC-US were regarded as positive.

VIA

In order to do VIA, acetic acid 5% was taken on the cervix, and then, the cervix was watched with naked eye behind the white light of a 100-W lamp after 30–60 s. In case a previously not white area in the cervix had turned white, VIA was considered as positive, and biopsy was taken from that area.

Colposcopy

In the next step, all the patients underwent colposcopy test 30–60 s after the cervix was moistened with acetic acid 5%; if suspicious points were seen with naked eye, biopsy was taken from these areas. In case the patient had normal colposcopy and no suspicious point was seen, biopsy was taken randomly from four areas of the cervix and sent to the pathologist.

Data Analysis

To analyze the data, descriptive (frequency, relative frequency, and central average index), analytical methods (evaluations of sensitivity and specificity) and SPSS software version 20 were used.

Results

Most cases included in this study were 20–40 years old, and 46.7% of them had diploma or associate degree. The highest incidence of immunodeficiency was associated with AIDS (19.3%), and the least incidence was related to multiple myeloma and ulcerative colitis (0.7%); 40% of them had a chronic disease, and more than 50% of them were smokers (Table 1). According to colposcopy and VIA tests, 77% and 77.8% of them had normal results, respectively (Table 2).

The biopsy results of 104 patients (77%) were normal. Twenty-one patients (15.6%) were CIN[1]1, 9 patients (67%) were CIN2, and 1 patient (0.7%) was CIN3. The Papanicolaou test results of 99 patients (73.3%) were normal. Twenty-eight patients (20.7%) were atypical squamous cell-undetermined significance (ASCUS), 4 patients (3%) were low-grade squamous intraepithelial lesion (LSIL), 3 patients (2.2%) were ASC-H, and 1 patient (0.7%) was high-grade squamous intraepithelial lesion (HSIL).

Sensitivity, specificity, positive predictive value and negative predictive value of colposcopy in comparison with those in biopsy were, respectively, 74.1%, 92.3%, 74.1% and 92.3%. Sensitivity, specificity, positive

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[1] Cervical Intraepithelial Neoplasia.

predictive value and negative predictive value of VIA in comparison with those in biopsy were, respectively, 67.7%, 91.3%, 70% and 90.4%. Sensitivity, specificity, positive predictive value and negative predictive value in Papanicolaou test in comparison with those in biopsy were, respectively, 54.8%, 81.7%, 47.2% and 85.8% (Table 3).

Sensitivity, specificity, positive predictive value and negative predictive value in combination of two methods (VIA and colposcopy) in comparison with those in biopsy were 83.8%, 86.5%, 65% and 94.7%, respectively (Table 4).

Discussion

A total of 135 patients with immunodeficiency who had referred to Afzalipour Hospital in Kerman, Iran, for cervical cancer screening were included in this study. Most of the patients were 20–40 years old (57%), which is a peak age for contagion of pre-cervical cancer lesions. Considering that this type of cancer has long precancerous conditions, recognizing precancerous lesions and providing appropriate diagnostic approach for the patients is very important.

The results of our study indicated that sensitivity, specificity, positive predictive value and negative predictive value of colposcopy were 74.1%, 92.3%, 74.1% and 92.3%, respectively. In Karimi-zarchi et al.'s study, the sensitivity, specificity, positive predictive value and negative predictive value of colposcopy were estimated as 66.7%, 98.94%, 80% and 97%, respectively [15]. Mahmoudi et al. in their study calculated the sensitivity, specificity, positive and negative predictive values of colposcopy 93%, 41.5%, 34.48% and 94.7%, respectively [16]. According to Bhattachan study, colposcopy had a sensitivity and negative predictive value of 100%, specificity of 85.5%, and positive predictive value of 50% [17]. Suguna study indicated a sensitivity of 95%, specificity of 60% and a false-negative value of 2% of colposcopy [18]. Maybe one of the reasons of the difference among colposcopy results in various studies is that prevalence of underlying cancer, manner of performing the test and interpreting the colposcopy findings, the experience of person who do colposcopy, and the threshold for dividing the results into normal and abnormal are all among the factors which can affect colposcopy results significantly.

In our study, sensitivity, specificity, positive and negative predictive values of VIA were calculated as 67.7%, 91.3%, 70% and 90.4%, respectively. Bhattachan indicated that sensitivity, specificity, positive and negative predictive values of VIA were 80%, 88.5%, 50% and 96.87%, respectively [17]. In another study on 100 patients, the sensitivity, specificity, positive predictive value and

Table 1 Demographic characteristics in patients with immunodeficiency (n = 135)

Variable		n	%
Age	20–40	77	57
	41–60	58	43
Level of education	Middle school degree and illiterate	46	34.1
	Diploma and associate degree	63	46.7
	Bachelor's and master's degrees	26	19.2
Type of disease	Breast cancer	12	8.9
	Colon cancer	6	4.4
	Lymphoma	4	3
	Multiple myeloma	1	0.7
	AIDS	26	19.3
	Rheumatoid arthritis	21	15.6
	Vasculitis	6	4.4
	Ulcerative colitis	1	0.7
	Lupus	23	17.1
	Kidney transplant	18	13.3
	Bone marrow transplant	17	12.6
Chronic disease	No	81	60
	Yes	54	40
Smoking	No	66	48.9
	Yes	69	51.1

Table 2 Distribution of diagnostic results of colposcopy and VIA in patients with immunodeficiency (n = 135)

Result of colposcopy and VIA	Colposcopy		VIA	
	N	%	N	%
Normal	104	77	105	77.8
Abnormal	31	23	30	22.2
Total	135	100	135	100

negative predictive value were reported 62.5%, 98.8%, 90.9% and 93.2%, respectively [19]. The difference of sensitivity and specificity in VIA in various studies may be due to the defect methodology and experience of the person who do test. Sometimes also, inflammation of the smears due to the inflammatory lesions getting acetowhite caused the high false-positive value in VIA. Accordingly, it is suggested that this method be combined with another method to do the screening. VIA is also a cheap, easy and tolerable test for the patient; it has high sensitivity; it gets immediate results, which reduces time waste; and it increases the patients' follow-up for the treatment [20]. Anyway, VIA is an effective screening method with noticeably comparable sensitivity and specificity, which can be used as a substitute screening method particularly in low-income countries that have high disease incidence [17].

In the present study, a sensitivity of 54.8%, specificity of 81.7%, positive predictive value of 47.2%, and negative predictive value of 85.8% were resulted in Papanicolaou test. In Karimi-zarchi et al.'s study, the sensitivity, specificity, positive and negative predictive values of Papanicolaou test were found to be 18.2%, 98.5%, 85.5% and 71.3%, respectively [15]. In Mahmoudi et al.'s study, the sensitivity, specificity, positive predictive value and negative predictive value in Papanicolaou test were 80.9%, 28.4%, 26.7% and 77.7%, respectively [16]. In another study on 100 patients, the sensitivity, specificity, positive and negative predictive values of Papanicolaou test were 23.5%, 100%, 100% and 86.5%, respectively [19]. However, although Papanicolaou test is an approved method for cervical cancer screening, some factors such as preparing and interpreting the findings can highly influence the final results. Maybe that is why the rate of sensitivity and specificity of Papanicolaou test differs in various studies. When Papanicolaou test gives intermediate and

Table 3 Distribution of diagnostic results of biopsy in patients with immunodeficiency based on colposcopy, VIA and Papanicolaou test

Results of colposcopy, VIA and Papanicolaou test		Biopsy		Sensitivity	Specificity	Positive predictive value	Negative predictive value
		Normal	Abnormal				
Colposcopy	Normal	96 (92.3)	8 (25.8)	74.1	92.3	74.1	92.3
	Abnormal	8 (7.7)	23 (74.2)				
VIA	Normal	95 (91.3)	10 (32.3)	67.7	91.3	70	90.4
	Abnormal	9 (8.7)	21 (67.7)				
Papanicolaou test	Normal	85 (81.7)	14 (45.2)	54.8	81.7	47.2	85.8
	Abnormal	19 (18.7)	17 (54.8)				

Table 4 Distribution of diagnostic results of a combination of VIA and colposcopy in patients with immunodeficiency ($n = 135$)

Results of combination of colposcopy and VIA		Biopsy		Sensitivity	Specificity	Positive predictive value	Negative predictive value
		Normal	Abnormal				
Colposcopy and VIA	Normal	90 (86.5)	5 (16.1)	83.8	86.5	65	94.7
	Abnormal	14 (13.5)	26 (84.9)				

indistinctive results, the need for complementary examinations for identifying probable underlying Neoplasia seems necessary. Examining the colposcopic appearance is one of the most appropriate available options in order to Papanicolaou test complementary review.

According to the results of this study, the diagnostic value of colposcopy in identifying cervical cancer was more than those of VIA and Papanicolaou test. The results of Karimi-zarchi et al.'s study indicated that colposcopy was better than Papanicolaou test in diagnosing cervical cancer [15]. Also, in Mahmoudi et al.'s study, colposcopy had higher sensitivity, specificity, positive and negative predictive values in identifying the initial phases of cervical cancer, when compared with Papanicolaou test [16]. However, in Suguna's study, although colposcopy was more sensitive due to its higher rate of false negatives, it had more specific cytology and had properties such as availability, low-cost training as an ideal screening test [18]. In Fakour et al.'s research, all patients underwent colposcopy in addition to the two tests of VIA and Papanicolaou test. The results showed that VIA works more effectively than cytology tests in identifying lesions and high-level dysplasias. The low rate of positive predictive value in VIA was due to the high false-positive results of VIA, which seemed to be due to defective training or low-skilled persons. With regard to their results, VIA is an appropriate test for cervical dysplasia screening; however, in order to minimize false-negative results in identifying dysplasia, it is better to use a combination of the two tests of VIA and Papanicolaou test [20]. This difference may be because predicting diagnosis by colposcopy needs practice and experience. In addition, the presence of different target groups in various studies causes discrepancy in the results regarding the effectiveness of different tests. Less sensitivity and specificity of Papanicolaou test in comparison with other methods raises the need for more quality control over stages of performing Papanicolaou test, such as sampling, preparing and interpreting samples. Moreover, abnormal Papanicolaou test is a sign of utilizing colposcopy, intrauterine curettage and cervix biopsy for identifying cervical cancer [8].

In our study, assessment of sensitivity and negative predictive value in the results of VIA and colposcopy showed that a combination of two methods is the most sensitive diagnostic approach for cervical cancer. In Mostafa Gharagaghi et al.'s study, a combination of three tests of Papanicolaou test, HPV and cervicography was the most effective diagnostic approach for patients with cervical cancer [21]. Accordingly, in order to increase the sensitivity and specificity of screening methods, a combination of these methods may be used.

In this study, the most cases of abnormal Papanicolaou test were related to ASCUS; it was consistent with the results of Mahmoudi et al. They had 18 patients who were ASCUS in Papanicolaou test (32.72%) [16]. In Karimi-zarchi et al.'s study, 4 patients were ASCUS in Papanicolaou test [15]. This result was not of concern, because all of them were reported as CIN1 or normal in biopsy [15]. In Bajaj's study, 5.5% of Papanicolaou test results were ASCUS [22].

In our research, the most frequency of immunodeficiency was noted among patients with acquired immune deficiency syndrome (AIDS). The studies done in USA showed that 29–30-year-old women living in areas of high outbreak of HPV and HIV are more susceptible to cervical cancer [23]. Leibenson et al. studied 84 women were infected with HIV virus, and their results indicated that women infected with HIV and with immune deficiency are susceptible to cervical cancer, but the exclusive screening programs for these patients have not been performed yet [24]. Therefore, although cervical cancer is aggressive, it is preventable, provided that cancer screening special for women infected with HIV is done [23].

Conclusion

In the present study, colposcopy was shown to have a higher level of sensitivity, specificity, positive and negative predictive values, in comparison with Papanicolaou test and VIA. Since cervical cancer is the most common women's cancer in developing countries, the efficiency and affordability of different methods of cervical cancer screening in women should be assessed in more extensive studies, to enable identifying the most effective diagnosing methods and arrange comprehensive screening programs on their basis.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This study was approved by the Ethics Committee of Kerman University of Medical Sciences in Iran (Ethical Code: IR.KMU.AH.REC.1397.045).

Consent to Participate Informed consent was taken from all patients.

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