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Research Article

Colposcopy to all: does this Approach increases Detection Rate of Preneoplastic Cervical Lesions in Cases with High Risk Hpv.

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Abstract

Objectives: It was aimed evaluate the benefit of colposcopic examination in the determination of cervical intraepithelial neoplasia (CIN) 2 and above lesions (CIN2+) including CIN2, CIN3, and cervical cancer in cases with high-risk HPV types other than HPV 16 and 18, and having normal Pap smear cytology results in national screening programme.

Methods: Group 1 (n:128) was formed of cases with either HPV 16 and/or 18 positive, with/without other high-risk HPVs. Group 2 (n:149) included cases determined as positive only for other high-risk HPV types without HPV 16 and/or 18. All participants underwent colposcopic examination.

Results: In a total of 98 cases determined with CIN2+ lesions on colposcopy, 51 cases (52.0%) were reported as normal cytology, and 47 (48%) cases as abnormal cytology in the Pap smear results. In cases with normal Pap smear screening, the detection rates of CIN2+ on colposcopy were 36.8 and 19.5% in Groups 1 and 2 respectively (p=0.026).The Pap smear screening was determined to have sensitivity of 42.6% specificity of 81.1% positive predictive value of 4.0, and negative predictive value of of 98.7%.Malignancy was determined in a total of 7 patients (5 in Group 1, 2 in Group 2.

Conclusions: Routine application of colposcopy not only to HPV 16 and 18 but also to other high-risk HPV types, with normal Pap smear screening could contribute to increasing the detection rates of high risk lesions. The findings of the current study could be useful to revise guidelines related to cervical cancer screening.

Keywords: High Risk Hpv, Pap Smear, Cervical İntraepithelial Neoplasia and Colposcopy.

1. Introduction

Cervical cancer is the fourth most commonly seen cancer in females worldwide, with 430,000 diagnoses of invasive cervical carcinoma per year and 260,000 deaths per year related to cervical cancer [1]. Papilloma viruses are members of the Papilloma virus family with a double-chain DNA structure. As these viruses are species-specific, human Papilloma viruses (HPV) of this family only cause infection in humans [2].

Many HPV genotypes, including 16, 18, 26, 31, 33, 35, 39, 45, 51, 53, 56, 58, 59, 66, 68, 73, and 82, associated with cancer and these are known to be high-risk, cancerogenic or cancer-related. Almost all cervical cancer cases can be attributed to HPV infections, and HPV 16 is responsible for 50% of cases and HPV 18 for 20%.HPV 16 is the most commonly seen member of this group and has the highest risk of progression to cancer [3, 4]. HPV types 31, 33, 45, 52, and 58 have been reported to cause cervical cancer at the rate of 19% [5].

Various methods are used in the evaluation of the cervix, including smear tests, cytology, co-test, colposcopic examination and conization[6]. In the 2012 ASCCP guidelines, the application of colposcopy is recommended even when the Pap smear test is normal in the presence of HPV 16 and 18. In the presence of other high risk HPV genotypes, it is suggested to perform colposcopic examination if there is an abnormal Pap smear result [7].

In 2019 ASCCP guideline, colposcopy is recommended if combination of current results and past history (including unknown history) of a patient yields a 4.0% or greater

probability of finding CIN 3+ [8]. The aim of this study was to compare the smear, colposcopy and if performed conization results following the application of colposcopy to all patients determined with high risk HPV positivity in cervical cancer screening, irrespective of the Pap smear result. Thus it was aimed to contribute to the updating and development of management protocols for high-risk HPV types other than HPV 16 and 18 in cervical cancer screening.

2. Methods

This case-control study included 277 HPV-positive patients who presented at the Gynaecology Oncology Clinic of a tertiary level reference hospital between 2019-2020. Informed consent was obtained from all the patients for participation in the study. Approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaraş Sütçü İmam University Hospital (Institutional Ethics Committee approval number: #04-2019708).Patients were excluded from the study if they had previous abnormal pap smear screening, undergone procedures such as cervical ablation or conization because of a diagnosis of cervical intra-epithelial neoplasia, if they undergone hysterectomy, had a diagnosis of genital cancer, had severe immune deficiency, or rejected colposcopy examination.

2.1. Data and Sample Collection and Studies

Since 2014, the Turkish Ministry of Health has conducted high-risk HPV typing in cervical smear samples (co-test) taken from women aged 30-65 years in every 5 years in centers known as KETEM, as a part of national cervical cancer screening programme. Cases determined with high-risk HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 62, 66, 68, 70, 81, 83, 84) in this screening program are accepted as screening-positive, and are referred to second and tertiary level centres for diagnostic tests, follow-up and treatment.

The Pap smear samples in this study were acquired with the conventional method by trained nurses and the test results were reported using the 2001 Bethesda system [9]. According to this system, the cytology results are classified as atypical squamous cells of undetermined significance (ASC-US), atypical glandular cells (AGC), low-grade squamous intra-epithelial lesions (LSIL), high-grade squamous intra-epithelial lesions (HSIL), adenocarcinoma in situ (AIS), and squamous cell cervical cancer (SCC). Cases with any one of these results in the Pap smear screening were accepted as an abnormal smear result. Patients were classified in two groups according to the Pap smear test result as normal or abnormal cervical cytology.

Independently of the smear test result, colposcopic evaluation was applied to all the patients by the same clinician (K.G). Based on the pathologic reports of the colposcopic biopsies and conization, cervical intraepithelial neoplasia (CIN) 2, 3 and cancer were accepted as CIN2 and above lesions. In the cases applied with conization, theloop electrosurgical excision (LEEP) procedure was used. Conization was applied when there was incompatibility between the cytology and histology results, inadequate colposcopic evaluation, determination of malignancy in the colposcopic biopsy or in the endocervical results,no determination of a lesion in the colposcopic evaluation despite an HSIL smear result or as a treatment modality for CIN2 and CIN3.

The cervical cancer screening results from the KETEM centre were used for HPV typing. Group 1 (n:128) was formed of cases with positivity in respect of either one of HPV 16 and/or 18, or positivity for other high-risk HPVs together with these types. Group 2 (n:149) included cases determined as positive only for other high-risk HPV types without HPV 16 and/or 18. Cervical smear samples were collected for HPV-DNA examination. In compliance with the national HPV laboratory working principles, the accepted sample transport medium (STM) and smear samples were kept in a water bath at 65°C for 45 mins, and were then converted to single-chain DNA form by passing through the denaturation procedure. Subsequently the samples were separated as HPV positive or negative by examination with the Digene HPV HC2 DNA test kit (Qiagen, Hilden, Germany) in a DML 3000 luminometer device in the Rapid Capture System of the laboratory.

For DNA isolation in the samples, PCR was applied using an EZ1 Advanced Isolation device and EZ1 virus mini kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. For genotyping, preparation was made with the Clart HP2 PCR kit (Genomica, Madrid, Spain) and strips were read with a microarray system. Samples from which a result could not be obtained were placed in a Qiagen Rotor-Gene Q Real Time device (Qiagen, Hilden, Germany) and results were obtained. Confirmed HPV positive isolates were stored for 5 years in a cold room at -20°C.

2.2. Statistical Analysis

Data obtained in the study were analyzed using IBM SPSS vn. 22 software. Conformity to normal distribution of quantitative variables was examined with the Kolmogorov-Smirnov test. Categorical variables were compared with the Chi-square test. In the comparison of two groups of data showing normal distribution, the Student's t-test was applied and for data not showing normal distribution, the Mann Whitney U-test. In multiple group comparisons, the One-Way Anova test was applied to data with normal distribution, and the Kruskal Wallis test to data not showing normal distribution. Continuous variables were stated as mean ±standard deviation (SD) values and categorical values as number (n) and percentage (%). A value of $p<0.05$ was accepted as statistically significant.

3. Results

No statistically significant difference was determined between Group 1 and Group 2 in respect of age, mean gravida and parity ($p>0.05$ for all). According to the Pap smear test results, 62.7% of the cases with abnormal cytology were determined in Group 1 and 37.3% in Group 2 ($p<0.001$). Significantly fewer cases in Group 1 were determined with a normal smear result compared to Group 2 (59.4% vs 79.2%, $p<0.001$) (Table 1).In cases with normal Pap smear screening, the detection rates of CIN 2+ on colposcopy were

36.8% and 19.% in Groups 1 and 2 respectively (p=0.026). In comparison of cases with abnormal Pap smear results, Groups 1 and 2 were found to have CIN2 and above lesions in 69.2% and 35.5% of the cases respectively (p=0.005). In a total of 98 cases determined with CIN 2 and above lesions on colposcopy, 51 cases (52.0%) were reported as normal cytology, and 47 (48%) cases as abnormal cytology in the Pap smear results.

In the colposcopic evaluation, malignancy was determined in 2 cases (2.7%) in Group 1, one of which had a normal cytology report from the Pap smear test and the other was reported as abnormal cytology.

In the conization results, cervical cancerwas determined in 5 more cases in addition to the 2 cases determined with colposcopy. Of these 5 cases, 3 were in Group 1, and 2 in Group 2. One of the 2 cases in Group 2 determined with cervical cancer was HPV 31-positive and the other case was HPV 45 and 58-positive. All of the 5 cases determined with malignancy with the conization procedure, had CIN 3 in colposcopy. Of the CIN 2 and above lesions determined in conization, 98.3% were reported as CIN 2 and above lesions and the remaining 1.7%as CIN1 lesion in colposcopy.

When the age of the participnts was stratified into decades as 30-39, 40-49 and so on, no difference was detected inbetween age groups regarding the results of the pap smear screening, colposcopy and conization (p>0.05 for all).

In the determination of low and high-grade lesions in patients with high-risk HPV, the Pap smear test was determined to have sensitivityof 42.64% (95% C1:33.97% to 51.64%), specificityof 81.08% (73.83% to 87.05%), positive predictive value (PPV)of 3.97%(95% C1: 2.72% to 5.74%), and negative predictive value of (NPV) of 98.72% (95% C1: 98.49% to 98.92%) (Table 2).

4. Discussion

The results of the current study showed that high risk HPV types other than HPV 16 and 18 were associated with a high rate of high grade cervical dysplastic lesions albeit normal Pap smear cytology. In a study of samples obtained from 14,249 women, De Sanjose et al reported that HPV types 31, 33, 45, 52, and 58 were the agent in 19% of cervical cancer cases, and HPV 16 and 18 were responsible for 71% of invasive cervical cancers [10]. In accordance with these data, in the current study HPV 16 and/or 18 types was determined in 5 (71.4%) of the 7 cases determined with malignancy, other types in 2 cases (28.6%). Five cases of cervical cancer which had been undiagnosed on colposcopy was determined by conization procedure.

Consistent with the data in literature, in the current study patients with HPV 16 and/or HPV 18 with a pathological smear result, the rate of CIN 2 and above lesions determined was significantly higher than in cases with other HPV types (69.2% vs 35.5%). CIN 2 and CIN3 lesions are high grade lesions having a risk of progression to invasive cancer [11]. Since it is not known which patients with high grade lesions would develop cancer, it is of paramount importance to detect and treat high grade lesions. Therefore, it is important that those high grade lesion are not missed in screening tests. However, in the current sudy, sensitivity andpositive predictive values of the Pap smear screening test were very low(%42.6 and 4.0% respectively).

In literature, different values have been reported for the diagnostic performance of the smear test. In a meta-analysis including 62 studies, Papsmear sensitivity and specificity were reported as 11-99%, and 14-97% respectively [12]. Similar to our results,low sensitivity and PPVvalues and high specifity and NPV values were determined for pap smear screening (28.5%, 13.3%, 74% and 88.1% respectively) in a recent study [13]. False negative rates of Pap smear result vary from 20% to 44.9% [14]. Low sensitivity of smear screening is known to be due to various reasons such as differences in the technique of obtaining the smear, differences in the instruments used to collect the cells, and problems in transferring and fixing the cells to the slide [15]. H.Yerlikaya ve at all:One of the human papillomavirus genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 67 and 68 wasisolated in 19 (4.9%) of 383 female patients included in the study. human papillomavirus 16 was detected in five (26.3%)patients, human papillomavirus 18 was detected in one (5.2%) patient, and one of 13 other high-risk types was detectedin the remaining 13 (68.4%) patients.

The mean age of women with low-risk human papillomavirus genotype was 43.41±9.90 years, and the mean age ofwomen with human papillomavirus high-risk genotype was 41.79±8.70 years.According to the Bethesda 14 classification, normal cytology was detected in 354 patients, ASC-US in 19 (5%), ASC-H intwo (0.5%), LSIL in two (0.5%), HSIL in two (0.5%), AGC in 3 (0.8%) and one patient (0.3%) had adenocarcinoma in situ [16].

Knowing that it is not possible to prevent all of the cervical cancers by screening programs, overtesting or overtreatment should be minimized to maintain a balance between harm and benefit. As so, colposcopy is not recommended in high risk HPV types other than types 16 and 18 with normal Pap smear cytology [8]. In the current study, it was found that in the presence of other high-risk HPV types other than HPV 16 and 18, every one of 5 patients with normal pap smear result had CIN 2 and above lesions.This finding supports the application of colposcopy in all cases with high-risk other HPV DNA types even if the smear test screening result is normal in order to increase detection rate of cervical cancer and precancerous lesions.

5. Conclusion

In conclusion, in the presence of high-risk HPV DNA positivity other than HPV 16 and 18, CIN2 and above lesions were determined in approximately 1 in 5 cases on colposcopy despite normal cytology reported in the Pap smear test. Therefore, taking these false negative results of the smear test into consideration, routine colposcopic evaluation of all high-risk HPV DNA types could increase the determination and prevention rates of cervical cancer.

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A list of Abbreviations

- CIN: cervical intraepithelial neoplasia
- HPV:human Papilloma viruses
- ASC-Us: atypical squamous cells of undetermined significance
- AGC: atypical glandular cells
- LSIL: low-grade squamous intra-epithelial lesions
- HSIL: high-grade squamous intra-epithelial lesions
- AIS: adenocarcinoma in situ
- SCC: squamous cell cervical cancer
- LEEP: loop electrosurgical excision
- DNA: deoxyribonucleic acid
- PCR: Polymerase chain reaction

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