RESEARCH ARTICLE

Cost and Effectiveness Comparison of Immediate Colposcopy Versus Human Papillomavirus DNA Testing in Management of Atypical Squamous Cells of Undetermined Significance in Turkish Women

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Abstract

Background: A small but significant proportion of cases with atypical squamous cells of undetermined significance (ASCUS) may harbour CIN 2-3, or even invasive carcinoma. Although immediate colposcopy, HPV-DNA testing or expectant management are three recommended options in ASCUS triage, a consensus does not currently exist on which one of these approaches is the most efficient. In this study, we aimed to compare the performance and cost of immediate colposcopy and colposcopy based on the human papillomavirus (HPV) testing for detecting histologically confirmed high-grade cervical intraepithelial neoplasia (CIN) in women with ASCUS. Materials and Methods: Records of 594 women with an index Papanicolaou smear showing ASCUS were retrospectively analyzed. Women in the immediate colposcopy arm were referred directly to colposcopy (immediate colposcopy group, n=255) and those in the HPV triage arm were proceeded to colposcopy if the high-risk HPV (hrHPV) test was positive (HPV triage group, n=339). High grade CIN (CIN2+) detection rate and treatment costs were compared between the groups. Results: The detected rate of CIN2+ was higher in the HPV triage group compared to immediate colposcopy group (8% vs. 1.6%, p=0.011). In the HPV triage group, the total cost, cost per patient, and the cost for detecting one case of high grade CIN were higher than the immediate colposcopy group (p<0.001). Conclusions: In women with ASCUS cytology, HPV DNA testing followed by colposcopy is more costly than immediate colposcopy, but this approach is associated with a higher rate of CIN2+ detection. This findings suggest that HPV DNA testing combined with cervical cytology could reduce the referral rate to colposcopy

Keywords: Colposcopy - HPV testing - ASCUS - CIN - Turkey

Introduction

Cytology-based screening programs for precancerous lesions of the cervix has significantly decreased the incidence of cervical cancer (Gustafsson et al., 1997). However, cytological examination has limited sensitivity and specificity for detecting high-grade cervical intraepithelial neoplasia (CIN), the precursor of cervical cancer (Nanda et al., 2000). Epidemiologic studies have shown that infection with carcinogenic types of human papillomavirus (HPV) represents a nearly universal event in the pathogenesis of CIN and invasive neoplasia (Bosch et al., 1995; Nobbenhuis et al., 1999). This well-established knowledge has led to the development of diagnostic applications for HPV testing. There are clear benefits for the use of HPV testing in the detection of

abnormal cervical cells for cervical cancer (Naucler et al., 2009), and the management of women with equivocal smears (Cuzick et al., 2003; Arbyn et al., 2004). Therefore, HPV testing has been advocated for use in addition to cytology (Brink et al., 2006).

Only colposcopy-directed biopsy can definitively identify women with CIN 2 or 3. Consensus exists that women with high-grade cytologic lesions require further evaluation with colposcopy. However, optimal treatment option for women with atypical squamous cells of undetermined significance (ASCUS) is not well established (Schiffman and Solomon, 2003; Arbyn et al., 2004). Most low-grade lesions regress spontaneously. Referral to the immediate colposcopic examination results in substantial costs in these cases (Arbyn et al., 2004). On the other hand, a small but significant proportion of

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cases with ASCUS may harbour CIN 2-3, or even invasive carcinoma (Schiffman and Solomon, 2003; Arbyn et al., 2004).

This study was conducted to compare the performance and cost of the immediate colposcopy versus HPV DNA testing for referral to colposcopy, in the initial management of ASCUS to detect cervical intraepithelial neoplasia grade 2 or greater (CIN 2+). The prevalence and distribution of high- risk HPV types and their relation to histologic diagnoses were also assessed.

Materials and Methods

Study design

This retrospective study comprised women diagnosed with ASCUS on Papanicolaou (Pap) smear between June 2009 and December 2010, who were referred the gynecologic oncology unit of Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey. Women who were pregnant or had been previously treated for CIN were excluded. Cases where the cytologic and histologic specimens were deemed insufficient for diagnosis were also excluded from the analysis. The study was approved by local instutional review board, and informed consents were obtained from all participants.

Two study groups were identified according to triage method after diagnosis of ASCUS: Women in the immediate colposcopy arm (directly underwent colposcopy)and the HPV triage arm (underwent colposcopy if had high-risk (hr) HPV DNA positivity).

Cytology

Cervical cytology samples were obtained by using a cytological brush. Conventional cytologic examination with Papanicolaou stain was performed. Slides were evaluated by experienced cytopathologists. Cytologic findings were classified according to the 2001 Bethesda System.

HPV DNA testing

Cervical brush specimens were collected in Cell Collection Media (Cobas® PCR, Roche Diagnostic GmbH, IN, USA). DNA was purified with the Magna Pure DNA isolation kit I on the MagNa Pure LC System (Roche Diagnostics, IN, USA). After nucleic acid isolation, all samples were analyzed by Roche Linear Array HPV Genotyping Test (Roche Diagnostics, IN, USA) for polymerase chain reaction (PCR) amplification of target DNA, followed by nucleic acid hybridization using a reverse hibridization system for the simultaneous detection of high risk HPV genotypes (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 82).

Colposcopic examination

Colposcopic examinations were performed using a video colposcope (Welch Allyn® Video Colposcope Model No: 88002A, Welch Allyn®, NY,USA) by a gynecologic oncologist. After initial colposcopic examination under low and high magnification, vascular structure of the cervix was assessed with green filter. Cervix was then rinsed with a 3% solution of acetic acid for 1 min. Areas that were suspicious for CIN were biopsied under colposcopic guidance. Endocervical curettage (ECC) was performed in all cases. All specimens were evaluated by trained cytopathologists who were blinded to the results of HPV DNA testing.

Histologically confirmed CIN2+ was chosen as an endpoint of the study. Subsequent treatment and follow up of the women with abnormal histologic diagnoses were performed according to The American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines.

Costs

Direct medical costs were identified and calculated in Turkish money currency (TL) for each participant, and then converted to European money currency (Euro). These included costs for Pap test, HPV test, office visit, colposcopy, cervical biopsy and pathological examinations.

Statistical analysis

Data analysis was performed using SPSS for Windows version 11.5 statistical package program (SPSS, Inc., Chicago, IL, USA). Continuous data were expressed as mean±standard deviation (SD) or median (minimum-maximum). The Shapiro-Wilk test was used to establish whether the continuous variables were normally distributed. If the normality assumption for the comparison of means between two groups was satisfied, Student's t-test was applied for the comparisons of means. Alternatively, if there was evidence of non-normal distribution, Mann–Whitney U test was used. Categorical data were presented as number and percentage, and were analyzed by Pearson's chi-square or Fisher's exact test. A P-value less than 0.05 was considered as statistically significant.

Results

A total 594 patients with the cytologic diagnosis of ASCUS were included in the study. Two hundred fifty-five women were assigned to the immediate colposcopy group and 339 were assigned to the HPV triage group. Mean ages of all patients, immediate colposcopy group and HPV testing groups were 42.8±10.3, 43.5±10.2 and 42.4±10.2 years, respectively (range 21-71). There were no significant differences in terms of age between the study groups.

All of the women in the immediate colposcopy group underwent colposcopic examination, colposcopy

Table 1. Distribution of Histological Results Among Study Groups

	Immediate colposcopy group (n:255)	HPV triage group (n:75*)	p value
Negative (n,%)	204 (80.0%)	51 (68%)	>0.05
CIN1 (n,%)	47 (18.4%)	18 (24%)	>0.05
CIN2+ (n,%)	4 (1.6%)	6 (8%)	0.01

*Referred to colposcopy, due to high-risk HPV DNA positivity

directed cervical biopsy and ECC. Of the 339 women included in the HPV triage group, 75 (22.1%) were high- risk HPV positive, and subsequently underwent colposcopic examination, cervical biopsy and ECC. In the immediate colposcopy group, vast majority of the women had negative findings for high grade CIN. Eighty percent had benign findings such as cervicitis, squamous metaplasia (80%) or CIN 1 (18.4%). Four women had CIN2+ (1.6%). In the HPV triage group, most of the women had also negative (68%) or CIN1 (24%) histologic findings. Compared with immediate colposcopy, HPV testing increased the rate of colposcopic findings that were CIN2+ (n=6, 8%) (p=0.011). Table 1 demonstrates the distribution of histologic results between the groups. When the percentage of final diagnosis of CIN2+ was compared between the immediate colposcopy group and women of HPV triage group (n=339), no significant differences were found (p>0.05). Overall, the most common high-risk HPV types were types 16 (n=19, 24.7%), 52 (n=13, 16.9%) and 51(n=11, 14.3%). Among women with CIN2+ histology, the most common high-risk HPV type was type 16 (n=4, 66.7%).

The total cost (€87,952 vs. €26,608), cost per patient (€259.1 vs €104.3) , and the cost per one HGSIL diagnosis (€14,654 vs. €6,652) were significantly higher in the HPV triage group (p<0.001).

Discussion

In this study, rate of histology-confirmed CIN2+ diagnosis was higher in patients with positive HPV DNA testing followed by colposcopic biopsy compared with colposcopy alone in the management of ASCUS cytology. HPV DNA testing is a promising option for primary screening of cervical cancer (Kim et al., 2005). There are also clear benefits for the use of HPV testing in the triage of equivocal smears (Manos et al., 1999; Cuzick et al., 2008). The relevant literature indicates that HPV DNA testing has improved accuracy than repeat Pap smear using the threshold of ASCUS for detecting high-grade CIN (Manos et al., 1999; Solomon et al., 2001; Arbyn et al., 2004).

The ASCUS and LSIL Triage Study (ALTS) is a multicenter randomized trial (1997-2001) that was designed to evaluate three management strategies for detection of CIN3 or invasive cancer cancer, in a population of women referred for evaluation of ASCUS or LSIL cytology (Kinney et al., 1998; Solomon et al., 2002; Schiffman and Solomon, 2003). This trial suggested that, HPV DNA testing followed by referral to colposcopy of only those women with oncogenic HPV is as effective as immediate colposcopy. The analysis of the ALTS data also demonstrated that HPV DNA testing had a sensitivity of 96% for detecting HSIL and a negative predictive value of 98%. Repeat cytology examinations were as sensitive as HPV DNA testing for detecting CIN3+, but would require more follow-up visits. Kulasingam et al. (2006) conducted a cost-effectiveness analysis of the ALTS trial to determine whether HPV DNA testing is a cost-effective alternative to immediate colposcopy or conservative management (Kulasingam et al., 2006). Their results confirmed that

the triage based on a positive HPV DNA test detected more CIN3+ cases and was less costly than immediate colposcopy or conservative management with up to three repeat cytology visits with HSIL+ as the threshold for referral to colposcopy. Another study reported that HPV DNA testing provides clinical benefits similar to those of immediate colposcopy with less associated costs (Kim et al., 2002).

Similar with these studies, we found that more cases of CIN2+ were identified, if women were referred to colposcopy on the basis of positive high risk HPV result. On the other hand, our study failed to demonstrate a lower cost of this management strategy. A plausible explanation for this lies with the assumption that, the cost of HPV DNA testing is higher than the total cost of cytology, colposcopy, and screening visits in Turkey.

Our study was not without limitations. Firstly, our study population was not limited to young women, in which HPV infections are more commonly encountered. A previous study demonstrated that primary screening with HPV DNA testing results in a significantly increase in detection rate of CIN2+ among women younger than 35 years of age (Ronco et al., 2006). Because our hospital is a referral center receiving a large number of patients, patients from all age groups were referred to our gynecologic oncology department for ASCUS cytology. Nevertheless, most of the patients included in this study were younger than 50 years of age. Secondly, our study did not include repeat cytology as a triage option for patients with ASCUS. This was due to our institutional policy for triage of ASCUS. Colposcopic examination is a widely performed procedure and repeated cytologic examination alone is not used routinely for triage of patients with ASCUS or LGSIL cytology at our institution.

In summary, according to our study results HPV DNA testing is associated with more cases of histologically confirmed high grade CIN than immediate colposcopy in women who had ASCUS on initial Pap smear. This finding favors HPV DNA testing in women with ASCUS. This approach could subsequently reduce the referral rate to colposcopy, however it could also result in increased cost for management of these cases. Future studies from different countries are needed in order to reach a final conclusion on the efficiency and cost comparison of the management strategies for patients with ASCUS.

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