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A real-time optoelectronic device in screening of cervical intraepithelial neoplasia

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Objective: The purpose of the study was to evaluate the sensitivity and specificity of the TruScreen in the diagnosis of cervical intraepithelial neoplasia (CIN) and the benefit of an adjunct test to cervical cytology screening.
Methods: Data were collected prospectively on 249 women who had undergone a loop electrosurgical excision procedure (LEEP) or hysterectomy at Kangnam St. Mary's Hospital of Catholic University between March and December 2008. The TruScreen was performed on 249 patients and the sensitivity and specificity were determined. The accuracy of TruScreen and cervical cytology were also ascertained.
Results: A remarkable improvement in the accuracy of the combined test for CIN 1 (sensitivity, 96.8%) and CIN2/3 (sensitivity, 92.4%) was noted. The sensitivity of TruScreen for CIN1 and CIN2/3 was 75.8% and 77.3%, respectively. The specificity of TruScreen for normal tissue was 85.1%.
Conclusion: The present study suggests that the TruScreen is an excellent device as an adjunctive test for the detection of CIN. The instantaneous result of TruScreen in women with ASCUS or LSIL can provide rapid and reliable information.

Key words: Screening; CIN; Sensitivity; Specificity

Introduction

Cervical cancer is the second most common female malignancy worldwide.[1] The cervix is easily accessible and the incidence of cervical cancer has been reduced by the Papanicolaou (Pap) test in developed countries.[2] The sensitivity of the Pap smear changes ranges from 30% to 87%; the low sensitivity of the Pap smear can be an obstacle to a successful cervical cancer screening program.[3,4]

The HPV DNA test, along with a Pap smear, has been investigated in an effort to improve the overall sensitivity of cervical cancer screening.[5] Unfortunately, the time required to receive the results of HPV DNA tests can result in significant anxiety to the patient with abnormal cytology.[6]

The TruScreen (Polartechnics, Sydney, Australia) is an optoelectric device which can detect cervical dysplasia and cancer instantly, and offers clinicians an opportunity to counsel patients immediately.[7] The TruScreen device consists of a probe and a console which are connected to each other by a cable. The electrical and optical assessment of the cervix detected by the probe is sent to a microcomputer in the console and compared with the data of 14 tissue types studied previously. Then, the type of cervical tissue is diagnosed and the results are expressed as "normal" or "abnormal" on the printed paper.[8]

The purpose of the current study was to evaluate the sensitivity and specificity of the TruScreen in the diagnosis of cervical intraepithelial neoplasia (CIN) and the benefit of an adjunct test to cervical cytology screening.

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Materials and Methods

Study population

Data was collected prospectively on 249 women who had undergone the loop electrosurgical excision procedure (LEEP) or hysterectomy at Kangnam St. Mary's Hospital of Catholic University between March and December 2008. The TruScreen was performed on women with abnormal Pap smears or patients who had undergone hysterectomy due to another gynecologic problem unrelated to cervical abnormalities. To evaluate the accuracy of the TruScreen, the pathology of the entire cervix was used as a gold standard. The TruScreen was carried out following liquid-based cytology (LBC), after which colposcopy or cervical biopsy were performed in patients who needed further evaluation. The results of the TruScreen did not affect the decisions regarding diagnoses and treatment of the cervix. The indications for LEEP of exocervical lesions in our study were biopsy-proven CIN on colposcopy; the indications for hysterectomy were known CIN, myoma uteri, endometriosis, and adenomyosis. This study was designed based on a prior investigation which had not detected cervical cancer,[9] so cervical cancer patients were excluded. Other exclusion criteria for the study were suspicious lesions of the endocervical canal, previous cervical biopsy or a history of LEEP, a prior complete hysterectomy, and current uterine bleeding. Written informed consent was obtained from each patient and the study was conducted with the approval of the institutional review boards.

TruScreen

The TruScreen is a portable optoelectronic instrument which was developed to detect cervical cancer and CIN. The cervical tissue is detected by a 17 cm pen-shaped probe with a 5 mm diameter, which consists of three peripheral electrodes and four central light emitters. The probe can be capped with a disposable sheath that contacts the cervix and prevents cross-infection (Fig. 1). The sensors on the tip combine reflected light and decaying electric current. The pulse (0.8 volts for 100 μ seconds) and four types of light are transferred to the cervix. During the examination of the color of the light on the probe is orange, and the probe should be placed perpendicular to the cervix and fixed on one spot. The distal tip of the probe can be moved to the next site on the cervix after the color of the light on the probe turns from orange to green. The normal result represents normal squamous epithelium or metaplasia, whereas an abnormal result indicates CIN or cervical cancer. If the number of examinations on the cervical tissue is <16, the result will be recorded as "inadequate".[8] The total time spent for the examination is <2 minutes.

Fig. 1. The appearance of TruScreen. TruScreen is a portable system which consists of a console and a pen-shaped probe. The size of the console is 38×19×7 cm and the length of the disposable white cap is 25 cm.

Study sample size

The study sample was classified into the following three categories based on the severity of cervical disease: normal, CIN1, and CIN2/3. The sample size was calculated on the previous results of the TruScreen for detection of normal cervix and CIN.[9]

Data collection and analysis

We recorded the patient name, age, pathology, cervical cytology, HPV test, type of operation, and results of TruScreen. If the diagnosis of the cervical biopsy differed from the entire cervix, the more severe pathology was selected for the final diagnosis. The accuracy of the TruScreen and adjunctive test combination was evaluated with a 95% CI according to the type of pathology of the cervix.

Results

Two hundred forty-nine women with CIN or normal cervices were recruited for the study. The mean (range) age of the study group was 41.9 (20~77) years. The proportion of normal cervices was similar to CIN (48.6% and 51.4%, respectively). Normal cytology was shown in 49.4% of all cases, and the most common type of abnormal cytology (32.5%) was a low-grade squamous intraepithelial lesion

(LSIL). Ninety-one of the 249 women were examined with a HPV genotyping test and 54 women were examined with hybrid capture. The 8 most common HPV types in the HPV typing test were, in descending order of frequency, 16, 58, 18, 52, 31, 39, 53, and 66 (Fig. 2). Table 2 shows the distribution of cytology according to the severity of the cervix. LSIL and atypical squamous cells of undetermined significance (ASCUS) were dominant types of cytology in CIN1, and 68.2% of CIN2/3 cases had a high-grade squamous intraepithelial lesion (HSIL) or atypical squamous cells (cannot exclude HSIL; ASC-H).

Table 3 shows the correct concordance of cervical cytology, the TruScreen, and the combination in cervical pathology. To overcome the diagnostic discrepancy between the Bethesda and CIN systems, we hypothesized that ASCUS of cytology corresponded to CIN1 and ASC-H corresponded to CIN 2/3. The false negative rate of Pap smears for CIN was 27.3%, and the sensitivities of the TruScreen for CIN1 and CIN2/3 were 75.8% and 77.3%, respectively. The specificity of the TruScreen for normal tissue was 85.1%. The combination modalities of the TruScreen and cytology were more sensitive for CIN than cervical cytology alone. A remarkable improvement in the sensitivity of the combined test for CIN 1 (sensitivity, 96.8%) and CIN2/3 (sensitivity, 92.4%) was

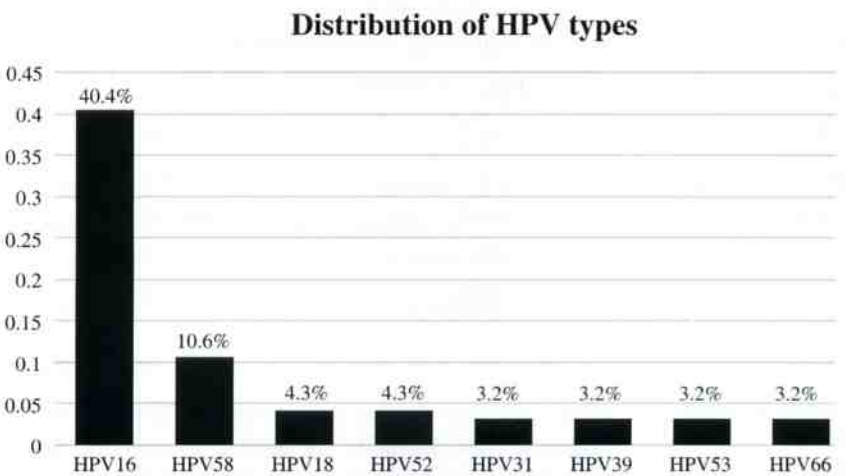

Fig. 2. The distribution of HPV types detected in CIN patients (N = 91).

Table 1. Characteristics of 249 women who entered into the accuracy study of TruScreen

Parameter			Results
Subjects			249 (persons)
Cervical pathology			
	Normal		121 (persons)
	CIN1		62 (persons)
	CIN 2/3		66 (persons)
Age			
	Mean		41.9 (years)
	Range		20~77 (years)
	Standard deviation		11.1
Operation type			
	LEEP		134 (persons)
	Hysterectomy		115 (persons)
HPV test			
	HPV DNA chip	single infection	78 (persons)
		multiple infection	13 (persons)
	Hybrid capture		54 (persons)

Table 2. Cytology distribution according to the cervical pathology grades in 249 women

Cytology \ Pathology	Normal (N=121)	CIN1 (N=62)	CIN2/3 (N=66)
Normal	112 (92.5%)	7 (11.3%)	4 (6.1%)
ASCUS	6 (5.0%)	14 (22.6%)	7 (10.6%)
ASC-H	0 (0%)	5 (8.1%)	14 (21.2%)
LSIL	3 (2.5%)	30 (48.4%)	8 (12.1%)
HSIL	0 (0%)	6 (9.7%)	31 (47.0%)
Cancer	0 (0%)	0 (0%)	2 (3.0%)

Table 3. Accuracy of TruScreen, cytology, and combined TruScreen + cytology according to the severity of cervical pathology (N = 249)

Accuracy \ Modality	TruScreen	Cytology	TruScreen + cytology combined
Specificity to normal	85.1%	92.0%	84.3%
95% CI	77.1~90.4	85.4~95.7	76.8~89.7
Sensitivity to CIN1	75.8%	74.2%	96.8%
95% CI	63.9~84.8	62.1~83.5	89.0~99.1
Sensitivity to CIN2/3	77.3%	71.2%	92.4%
95% CI	65.8~85.7	59.4~80.7	83.5~96.7

CI: confidence interval.

Table 4. TruScreen concordance with cervical pathology in women with ASCUS/LSIL cytology (N = 68)

	TruScreen	
Histology diagnosis	Negative (N =18)	Positive (N = 50)
Normal	1	8
CIN1	12	32
CIN2/3	5	10

noted. Table 4 shows the concordance between the histologic diagnosis and the result of the TruScreen in women with ASCUS or LSIL. The sensitivity of the TruScreen for CIN2/3 in ASCUS or LSIL cytology was 66.7%.

Discussion

Our results indicate that the accuracy of the TruScreen can compensate for the high false negative rate of cervical cytology in a screening program. The main causes of the relatively low sensitivity of the Pap smear are sampling and detection errors.[3] Cervical cancer can develop, even in women who have had Pap tests regularly,[10] and 17.5 % of cervical cancer patients have been reported to have had normal cytology less than 3 years before the detection of cancer.[11] Naturally, new methods are needed to support the inadequacies in screening programs for cervical cancer.

Various adjunctive tests to the Pap smear, such as colposcopy, cervicography, HPV DNA tests, and automated systems, have been introduced to improve the accuracy of conventional cytology.[12-16] The HPV DNA test was approved by the Food and Drug Administration as a screening method, along with cytology in women >30 years of age.[17] HPV type 16 was the most frequently observed in the current study (Fig. 2) and the literature supports our results.[18,19] A HPV DNA test 12 months after the diagnosis of a low grade lesion of the cervix shows the highest sensitivity for the detection of CIN 2 or 3.[20] If women learn of an abnormal Pap smear result, they are required to undergo evaluation several additional times to repeat the cytology or wait 5~7+ days to receive the results of additional tests. Women with abnormal cytology are reluctant to have a cervical biopsy because of cervical bleeding, pain, and infection.[21] Thus, there is a need for instant and non-invasive devices which can provide supplementary information to abnormal Pap smears.[22,23]

Based on the literature, TruScreen encourages women to participate in screening with the merit of lesser pain and

anxiety than conventional cytology,[7] and correlates with cervical pathology very well.[8] TruScreen also plays an adjunct role with Pap smears, thereby improving the sensitivity of Pap smears to 93%.[9] In the current study, the sensitivity of combined TruScreen and cytology was 96.8% for CIN 1 and 92.4% for CIN 2/3, which is higher than the previous report with TruScreen alone.[8] Also, these results are not inferior to the sensitivity of cytology combined with a HPV DNA test, cervicography, or colposcopy.[24-29]

HPV has a major role in the neoplastic morphology of CIN,[30] which affects the responsiveness of cervical tissue to optic and electric stimuli of the TruScreen probe.[9] The typical changes of CIN are disruption of the superficial cell layering and increasing the ratio of the nucleus to cytoplasm.[31,32] The tissue component shows its typical resistive and capacitive property, resulting in a different frequency and impedance in the electrical spectrum.[33,34] The Cole equation is used to measure the extracellular and intracellular conduction pathway. The normal squamous epithelium has no current passage around the cells, resulting in high resistance. From normal cervical tissue through CIN1 to CIN2/3, the extracellular current conduction increases with a reduction of normal squamous epithelium and the intracellular current conduction deceases with a rise of the nuclear to cytoplasm ratio.[35]

Cervical cancer can be diminished successfully if we know and manage the characteristics of pre-invasive disease of the cervix very well. LSIL and HPV-positive ASCUS act similarly in clinical situations and the subsequent risk of CIN2/3 is 27.6% and 26.7%, respectively.[36] Colposcopic- guided biopsy has revealed that 7.1% of ASCUS is more severe than CIN2.[37] Our study showed that 25.9% of ASCUS and 19.5% of LSIL corresponded to CIN2/3 on histologic diagnosis. As a result, further evaluation of mild abnormalities of the cervical cytology is an inevitable step to identify high grade lesions. TruScreen is considered to afford an instantaneous sensitivity of 66.7% for CIN2/3 to patients with ASCUS or LSIL.

This study had important limitations in that endocervical lesions and cervical cancer were not evaluated. However, this is the first study that examined the accuracy of the TruScreen with the entire cervical pathology.

The present study suggests that the TruScreen is an excellent device as an adjunctive test for the detection of CIN. The instantaneous result of the TruScreen in women with ASCUS or LSIL can provide rapid and reliable information.

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