Clinical results of a split sample liquid-based cytology (ThinPrep) study of 4,322 patients in a Turkish institution

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Summary

Purpose: A prospective study was carried out to compare the efficacy of liquid-based cytology (ThinPrep) with the conventional Pap smear using a split-sample design in a Turkish university hospital outpatient gynecology clinic.

Methods: 4,322 consecutive patients were recruited for the study between 2002 and 2003. All the patients underwent conventional Pap tests followed by a ThinPrep test for screening of cervical cancer. The results were evaluated in terms of the Bethesda III classification. All the patients with abnormal tests underwent colposcopy and directed biopsy.

Results: While 2.3% of the specimens were unsatisfactory for evaluation in the conventional Pap test group, this rate was 1.7% for the ThinPrep group. Epithelial cell abnormalities were observed in 42 (1.0%) patients in the conventional Pap test group and in 36 (0.8%) patients in the ThinPrep group. ASCUS was observed in 26 patients in the conventional Pap test group whereas the ThinPrep group had 20 cases of ASCUS as the leading cause of abnormal cytology. Biopsy of these cases revealed CIN 1 in two CIN 2-3 in three and cervical/endometrial adenocarcinoma in three patients. The ThinPrep application led to diagnoses of one additional case of CIN 2-3 and one case of adenocarcinoma among the negative or unsatisfactory for evaluation categories of the conventional Pap test group.

Conclusion: Despite an adverse bias introduced by the split-sample study design, application of ThinPrep showed an improved rate of specimen adequacy and increased sensitivity for more significant cervical precursor lesions over the conventional Pap test.

Key words: ThinPrep; Liquid-based cytology; Pap test; Cervical cancer.

Introduction

The Pap smear has been the most effective cancer screening test ever used since its introduction in the 1940s [1]. The widespread use of the Pap test has been largely credited for the drastic reduction in the incidence and mortality of cervical cancer in Western countries [2-6]. However, despite its efficacy, the conventional procedure has several drawbacks. Up to 30% of women with cervical cancer have been reported to have prior false-negative smears [7, 8]. Furthermore, meta-analyses of studies examining the efficacy of the Pap test have revealed a limited sensitivity for cervical cancer precursors [9, 10]. Thus, several new technologies have been introduced to improve the accuracy of the conventional Pap test. Liquid-based thin-layer technology is one of the newer methods developed to overcome the technical limitations of the conventional Pap smear [11]. Increased use of this technology has been observed in the last several years with improved sensitivity for cervical precursor lesions [12-15]. A prospective study was planned to compare the efficacy of liquid-based cytology (ThinPrep system) with the conventional Pap smear in a Turkish university hospital outpatient gynecology clinic.

Materials and Methods

A prospective study using a split-sample design was carried out to compare the efficacy of liquid-based cytology with the conventional Pap smear. Between January 1, 2002 and June 1, 2003, 4,322 consecutive patients were recruited for the study at Hacettepe University hospital outpatient gynecology clinic. The mean age of the patients was 41.5 ± 10.6 years (range: 17-87). All the patients underwent conventional Pap smears followed by a liquid-based thin-layer cytologic test for screening of cervical cancer. The ThinPrep system (Cytyc Corporation, Boxborough, MA, USA) was used for the liquid-based cytologic analysis. The conventional Pap test and ThinPrep test slides were examined by the co-author pathologists at the department of pathology. The results were evaluated in terms of the Bethesda III (2001) classification. Squamous cell abnormalities were categorized as ASCUS (atypical squamous cells of undetermined significance), ASC-H (atypical squamous cells- can not exclude HSIL), LSIL (low-grade squamous intraepithelial lesion) and HSIL (high-grade squamous intraepithelial lesion). Glandular cell abnormalities were categorized as AGC (atypical glandular cells), ACIS (adenocarcinoma in situ) and adenocarcinoma cells. All the patients with abnormal tests underwent colposcopy and directed biopsy when indicated. Histological results were categorized as CIN 1 (low-grade cervical intraepithelial neoplasia) and CIN 2-3 (high grade cervical intraepithelial neoplasia).

Statistical analyses were carried out using McNemar chi square and kappa tests.

Results

While 2.3% (n = 99) of the specimens were unsatisfactory for evaluation in the conventional Pap test group, this rate was 1.7% (n = 72) for the ThinPrep group (Table 1). Thus, use of ThinPrep achieved a 27% overall reduction which was statistically significant in the "unsatisfactory for evaluation" rate.

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Table 1. — *"Unsatisfactory for evaluation" rates.*

	Conventional		ThinPrep		p
	no.	%	no.	%	
Satisfactory Unsatisfactory	4,223	97.7	4250	98.3	0.02
	99	2.3	72	1.7	
Total	4,322	100	4322	100	

While 24 cases had unsatisfactory smears in both groups, 48 cases were read as unsatisfactory in only the ThinPrep group and 75 cases were unsatisfactory in only the conventional Pap test group (Table 2). The reliability of statistics in terms of unsatisfactory rate showed a significant correlation between the conventional and ThinPrep groups (kappa = 0.27, $p < 0.001$). When all unsatisfactory tests in both groups were excluded, general categorization of the cases revealed "negative for intraepithelial lesion or malignancy" in 96.7% of the conventional smears and 97.5% of the ThinPrep test group (Table 3). The reliability of statistics showed a significant correlation between the two groups in terms of negative results (kappa = 0.84, $p < 0.01$).

Table 2. — - *Correlation of unsatisfactory results in the conventional and ThinPrep groups.*

	ThinPrep		
Conventional	Satisfactory	Unsatisfactory	Total
Satisfactory	4,175	48	4,223
Unsatisfactory	75	24	99
Total	4,250	72	4,322

Table 3. — *General categorization in the conventional and ThinPrep groups.*

	Conventional		ThinPrep		p
Results	no.	%	no.	%	
Negative	4,181	96.7	4,214	97.5	0.04
Epithelial cell abnormality	42	1.0	36	0.8	
Total	4,223	97.7	4,250	98.3	

Epithelial cell abnormalities were observed in 42 (1.0%) patients in the conventional Pap test group and in 36 (0.8%) patients in the ThinPrep group (Table 4). The conventional group had a 16.7% increased rate of epithelial cell abnormality. Squamous cell abnormalities were ASCUS in 26, ASC-H in two and LSIL in two cases in the conventional Pap test group. The ThinPrep test group had 20 cases of ASCUS, two cases of ASC-H, nine cases of LSIL and two cases of HSIL. The ASCUS/SIL ratio was calculated to be 2.8 for the conventional test and 1.8 for the ThinPrep group. While glandular cell abnormalities were AGC in three and adenocarcinoma in two patients of the conventional Pap test group, the ThinPrep group had one case of AGC and two cases of adenocarcinoma.

Table 4. — *Epithelial cell abnormalities.*

	Conventional		ThinPrep	
Epithelial cell abnormalities	no.	%	no.	%
Squamous cells	37	0.9	33	0.7
ASCUS	26	0.6	20	0.5
ASC-H	2	0.0	2	0.0
LSIL	9	0.2	9	0.2
HSIL	–	–	2	0.0
Glandular cells	5	0.1	3	0.1
AGC	3	0.1	1	0.0
Adenocarcinoma	2	0.0	2	0.0
Total	42	1.0	36	0.8

A total of 46 patients were diagnosed with epithelial cell abnormalities in either the conventional or ThinPrep Pap test. Colposcopy and biopsy of these cases revealed CIN 1 in two, CIN 2-3 in three and cervical/endometrial adenocarcinoma in three patients (Table 5). Thus, 17.0% (8/47) of the patients with positive cytology had histologically confirmed cervical neoplastic lesions. The remaining patients did not have any evidence of cervical intraepithelial neoplasia. The ThinPrep application led to diagnoses of one additional case of CIN 2-3 and one case of adenocarcinoma among the negative or unsatisfactory for evaluation categories of the conventional Pap test group. Overall positive predictive value for histologically confirmed neoplasia was 14.2% (6/42) for the conventional Pap test group and 22.2% (8/36) for the ThinPrep group.

Table 5. — *Colposcopy and biopsy results in the conventional and ThinPrep groups.*

Results	Conventional Epithelial cell abnormality	ThinPrep Epithelial cell abnormality
Nonneoplastic	35	30
CIN 1	2	2
CIN 2-3	2	3
Squamous carcinoma	–	–
Adenocarcinoma	2	3
Total	42	36

Discussion

Results of a recent meta-analysis of 84 studies showed that the conventional cytology screening has a specificity of 98% and a sensitivity of 51% [16]. Since performance of the conventional Pap test was found to be lower than expected, efforts were undertaken to improve sensitivity. Liquid-based thin-layer technology was developed to address the five major limitations posed by the conventional Pap smear: failure to capture the entire specimen, inadequate fixation, random distribution of abnormal cells, obscuring elements, and technical variability in the quality of the smear [17-19]. The ThinPrep system is one of the products of liquid-based cytology currently available. Data regarding liquid-based cytology have indicated a significant benefit in the detection of cervical cancer precursors over the conventional Pap smear. The efficacy of liquid-based cytology has been assessed mainly by two types of studies including the split-sample and direct-to-vial designs. The split-sample studies accrue patients in whom a single sample collection is performed. The sample is initially used to prepare a conventional Pap smear and then the residual material on the collection device is rinsed in the collection media and sent for thin-layer preparation. This study design naturally suffers from a beneficial bias in favor of the conventional Pap smear [20]. Since the conventional Pap smear has been the standard of care for screening of cervical cancer in the

institution, the split-sample design was chosen for the current study. With this approach, it was aimed to allow adoption of the new technology at our institution. Similarly, earlier studies in the literature were using the split-sample-design whereas the most recent studies have adopted the direct-to-vial approach [21]. Following completion of the current study, routine application of ThinPrep could be available for screening of cervical neoplasia.

The use of ThinPrep significantly enhanced specimen adequacy by reducing the number of cases classified as unsatisfactory for evaluation in this series. Thus, the incidence of unsatisfactory samples dropped approximately one-fourth. The majority of split-sample studies in the literature resulted in a reduction of unsatisfactory samples [22-24]. The decrease of unsatisfactory samples leads to less recalls of patients for retest and contributes positively to the efficacy of new technology.

Examination of the data regarding the performance of liquid-based cytology showed that it outperformed the conventional Pap smear in the detection of cervical neoplasia [20-24]. However, the conventional Pap smear was able to identify slightly more cases of epithelial abnormalities in this series. This finding may be evaluated to be in contrast to the recent literature. Nevertheless, further analysis of subcategories showed that liquid-based cytology has an increased sensitivity for LSIL and HSIL with fewer cases in the ASCUS category. Consequently, use of ThinPrep characteristically leads to a decrease in the ASCUS/SIL ratio. This finding further supports the use of ThinPrep for screening of cervical neoplasia.

Although the conventional Pap test revealed more cases of epithelial cell abnormality, colposcopy and biopsy results showed two additional cases of histologically confirmed neoplasia in the ThinPrep group. The higher positive predictive value and superior detection of cervical/endometrial adenocarcinoma in this series also suggests the use of ThinPrep as the standard method for screening of cervical neoplasia as stated in the literature [25, 26].

Conclusion

Despite an adverse bias introduced by the split-sample study design, application of ThinPrep showed an improved rate of specimen adequacy and increased sensitivity for more significant cervical precursor lesions over the conventional Pap test.

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