Original Article

A Comparison of Conventional Pap Smear and Liquid-Based Cytology for Cervical Cancer Screening

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Abstract

Objectives: Early diagnosis and treatment of preinvasive lesions have made cervical cytology one of the most effective methods of cancer screening in industrialized nations, which have seen a sharp decline in the incidence and death of invasive cancer. The aim of this study is to compare liquid-based cytology (LBC) and conventional Pap on cervical smears.

Materials and Methods: From July 2018 to June 2022, 600 patients were included in this cross-sectional study, which was done at the Pathology Department of a Tertiary Care Facility in Western Maharashtra.

Results: Of the 600 patients, 570 (95%) had good conventional Pap smear (CPS), whereas 30 (5%) had poor ones. Five hundred and ninety-two (98.6%) LBC smears were satisfactory, whereas 8 (1.4%) were unsatisfactory. Endocervical cells were seen in 294 (49%) CPS, whereas 360 (60%) LBC smears showed endocervical cells. The morphology of inflammatory cells was similar in both techniques. Hemorrhagic background was seen in 212 (35%) CPS and 76 (12.6%) LBC smears. Only two samples showed diathetic background, which was seen on both CPS and smear. Out of the satisfactory smears in the case of CPS, 512 (85%) cases were reported as negative for intraepithelial lesion or malignancy (NILM), whereas 58 (9.7%) cases were reported as epithelial cell abnormality. In LBC smears, 526 (87.3%) were reported as NILM, whereas 66 (11%) were reported as epithelial cell abnormality. Organisms were detected in 208 (34%) CPS and 162 (27%) LBC smears. Screening time was 5 ± 1 min for CPS, whereas it was 3 ± 1 min for LBC smear.

Conclusion: Mortality will be decreased using LBC on a bigger scale in nations where many smears can be made and screened in a short amount of time, with the provision of doing human papillomavirus-based testing on the remaining sample.

Keywords: Cervical cancer, conventional Pap smear, liquid-based cytology

Introduction

The fourth most frequent disease in women worldwide and the second leading cause of cancer mortality among Indian women is cervical cancer.[1] This is a largely preventable cancer, through screening and vaccination. The slow-growing nature of cancer has been used as a tool for effective prevention through screening procedures and human papillomavirus (HPV) vaccination. One of the most effective methods of cancer screening in industrialized nations has been cervical cytology, which has led to a significant decline in the incidence and death of invasive cancer by the early identification and treatment of preinvasive lesions.[2-5]

The pathological course of invasive cervical carcinoma is prolonged. Early cervical abnormalities in the form of cervical intraepithelial neoplasia can be identified years before the onset of invasive cancer.[6] This is the fundamental idea behind cytological screening.[7]

The standard Pap smear test's specificity has been determined throughout time by several investigations to be about 98%–99%, although its sensitivity ranges from 50% to 75[8,9]

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or less[10] The standard Pap test has a number of drawbacks, including insufficient cell transfer to the slide, irregular distribution of aberrant cells, the presence of concealing inflammation and blood, and overlapped epithelial cells.[11,12]

To overcome these restrictions, liquid-based cytology (LBC) was presented as an alternative to traditional Pap in 1996. In the first generation of automated LBC, a suspension of cells is created by washing the sampling equipment into a vial of fixative. On a slide, a monolayer of cells is created from those. These slides are easier to analyze than traditional smears, and the leftover sample can be utilized for additional testing (HPV).

Two first-generation LBC technologies have received the Food and Drug Administration approval: ThinPrep[13] and SurePath[14] Other first-generation LBC technologies include Zhao *et al*.,[15] Singh *et al*.,[16] and Sharma *et al*.[17] Studies have shown that these procedures offer a variety of advantages over the traditional Pap smear. However, the expense of testing with these LBC techniques, which need a pricey automated device, limits their usefulness in impoverished countries. The majority of the instruments required by first-generation LBC procedures are no longer required by LiquiPrep, the second-generation LBC system. As a result, it provides a less expensive and easier alternative for cervical cancer screening. The LiquiPrep system consists of a cell base that serves as a membrane matrix, a fixative fluid vial, and a cleaning solution. This approach is appropriate for cervical cytology in underdeveloped countries because of its simple preparation process and high detection rate in comparison to traditional Pap[18,19] Other low-cost methods include manual LBC, semiautomated technology EziPrep, Turbitec (centrifugation onto a polylysine slide), Pap spin (cytospin-based smear preparation), and cytoscreen (centrifuge-based).[20]

Our study aimed to contrast conventional Pap cervical cytology with our low-cost LBC technique.

Materials and Methods

This cross-sectional study involved 600 patients and was carried out at the Pathology Department of a Tertiary Care Facility in Western Maharashtra between July 2018 and June 2022. The Institutional Ethics Committee (The research and recognition committee under the faculty of medicine at Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri) granted its ethical approval (IEC No. 1139).

Inclusion criteria

All females between 20 and 80 years of age were included in the study.

Exclusion criteria

Unwilling female patients, samples where either LBC or conventional Pap smear (CPS) of the same patient were not available for comparison, and patients who have received or are receiving chemo/radiotherapy.

The patient's informed consent was obtained before a thorough history was gathered. The patient underwent a physical examination, was placed in the lithotomy position, and a sample was taken. First, an Ayer's spatula was introduced into the cervix and gently turned 360° to acquire the specimens for conventional Pap. The material was then spread onto a slide that was free of oil and fixed in 95% alcohol. Smear was stained with Pap and H and E stains after fixing. Endocervical brushes provided by the manufacturer were similarly placed into the endocervical canal and spun 360° 3–4 times for LBC. The brush is then removed and put into a vial with fixative provided by the manufacturer for transportation. The vial is closed and shaken to obtain a homogenous mixing. To achieve a homogeneous mixture, the vial is closed and shaken. The laboratory receives the vial there. The slides were fixed in 95% ethanol before being routinely stained with Pap and H and E. Two pathologists independently examined the slides, along with a resident physician. According to the Bethesda method for reporting cervicovaginal cytology in use as of 2014, the smears were reported.

When necessary, the Chi-square test, simple percentage analysis, and unpaired *t*-tests were used to compare the two methods. *P* value <0.05 was regarded as statistically significant.

Results

Out of a total of 600 cases, 240 (40%) belonged to the third decade of life, 144 (24%) to the fourth decade, 140 (23%) to the fifth decade, 60 (10%) to the sixth decade, 12 (2%) to the seventh decade, and 4 (0.6%) to the eighth decade. The CPS and LBC smears were compared with respect to smear adequacy, representation (Endocervical cells), inflammatory background, hemorrhagic background, diathetic background, uniform distribution, cell overlapping, presence of artifacts, architectural and cellular morphologic changes, interpretation of results, detection of organisms, and screening time.

Out of the 600 cases, 570 (95%) CPS smears were satisfactory, whereas 30 (5%) were unsatisfactory. Of these, 12 smears had inadequate cellularity, whereas 18 smears were unsatisfactory due to obscuring of smear due to inflammatory cells or hemorrhage. 592 (98.6%) LBC smears were satisfactory, whereas 8 (1.4%) were unsatisfactory. All unsatisfactory cases were due to inadequate cellularity of smear. It was statistically significant that the specimen adequacy differed ($P < 0.05$). LBC smears produced more favorable smear results. The two methods did not differ in the cellularity of the smears in a statistically significant way ($P > 0.05$) [Table 1].

Endocervical cells were seen in 294 (49%) CPS smear, whereas 360 (60%) LBC smears showed endocervical cells. A statistically significant difference existed between the two methods ($P < 0.05$). LBC smears more commonly included endocervical cells.

Based on the appearance of the amount of neutrophils present, the degree of the inflammatory background was rated as mild, moderate, dense, and dense dirty. Compared to 440 (86%) cases of LBC, neutrophils were seen in 570 (95%) cases of CPS. With a $P < 0.05$, the difference was statistically significant. In CPS smears, the inflammatory background was more prevalent. Both approaches produced inflammatory cells with a similar morphology. In contrast to CPS, the neutrophils displayed higher clumping in LBC smears [Table 2].

Hemorrhagic background was seen in 212 (35%) CPS and 76 (12.6%) of LBC smears. A statistically significant difference existed between the two methods ($P < 0.05$). LBC smears revealed a background with less hemorrhage.

In our study, only two samples showed diathetic background (Diathesis is the result of necrotic tissue being broken down, which creates a granular, proteinaceous precipitate with variable staining. Malignant samples exhibit blood and its byproducts because the tumor tends to bleed as it degrades and ulcerates), which was seen on both CPS and smear. In contrast to 390 (65%) LBC smears, which had uniform cell distributions, just 72 (12%) CPS smears had them. With a more uniform distribution in LBC smears, this difference was statistically significant ($P < 0.05$).

Cellular overlapping was observed in 252 (42%) of LBC smears and 558 (93%) of CPS preparations. The findings showed that CPS smears had significantly higher cell overlapping, which was statistically significant ($P < 0.05$). The presence of artifacts was noted in 570 (95%) of CPS smears and 372 (62%) of LBC smears. Artifacts were clearly visible in CPS smears, and there was a statistically significant difference between the two methods. <0.05 is the *P* value.

Architectural and cellular morphologic changes were analyzed on the basis of cytoplasmic distortion, cell shrinkage/elongation, cytoplasmic vacuolization, imprecise cytoplasmic borders, and folding of cytoplasmic borders. Out of 600 cases, changes were seen concordantly in both techniques, i.e. 136 (22.6%) in CPS and 120 (20%) in LBC cases. Statistics showed that the difference was not significant ($P > 0.05$) [Table 3].

Interpretation of cytological diagnoses was done on the basis of Bethesda system 2014. Out of the satisfactory smears, In the case of CPS, 512 (85%) cases were reported as negative for intraepithelial lesion or malignancy (NILM), whereas 58 (9.7%) cases were reported as epithelial cell abnormality. In LBC smears, 526 (87.3%) were reported as NILM, whereas 66 (11%) were reported as epithelial cell abnormality [Table 4]. Interpretation of results was almost concordant between the two techniques. Statistics showed that the difference was not statistically significant ($P > 0.05$) [Table 5].

Organisms were found in 162 (27%) and 208 (34%) CPS smears, respectively. CPS smears showed greater detection. With a $P < 0.05$, this finding was statistically significant. *Doderlein bacilli* (normal commensals), *Gardnerella vaginalis* (shift in vaginal flora with clue cells), *Candida*, *Trichomonas vaginalis*, and herpes were the species identified. The detection of Doderlein and Gardenerella was higher in CPS 94 (45%) and 66 (31.7%), respectively, compared to LBC, 58 (27.8%) and 62 (29.8%). Candidal

Table 1: Comparison of cellularity

Cellularity	CPS	LBC	Chi-square test	DF	*P*
Adequate	588	588	0.41	1	>0.05
Inadequate	12	8			
Total	600	600			

LBC: Liquid-based cytology, CPS: Conventional Pap smear

Table 2: Comparison of inflammatory background

Inflammatory background	CPS	LBC	Chi-square test	DF	*P*
Mild	112	296	52.84	1	<0.00001
Moderate	212	104			
Dense	158	26			
Dense dirty	88	8			
Total	570	440			

LBC: Liquid-based cytology, CPS: Conventional Pap smear

Table 3: Comparison of architectural/cellular morphologic changes

Architectural/ morphologic changes	CPS	LBC	Chi-square test	DF	*P*
Present	136	120	1.9	1	=0.16
Absent	464	480			
Total	600	600			

LBC: Liquid-based cytology, CPS: Conventional Pap smear

Table 4: Comparison of cytological diagnoses

Diagnoses	CPS	LBC	Chi-square test	DF	*P*
Unsatisfactory	30	8	0.144	2	>0.05
NILM	512	526			
Epithelial cell abnormality	58	66			
Total	600	600			

LBC: Liquid-based cytology, CPS: Conventional Pap smear, NILM: Negative for intraepithelial lesion or malignancy

Table 5: Epithelial cell abnormalities

Epithelial cell abnormality	CPS	LBC
ASCUS	26	30
ASC-H	0	2
LSIL	12	14
HSIL	6	6
SCC	8	8
AGC-NOS	2	2
Adenocarcinoma	4	4
Total	58	66

ASCUS: Atypical squamous cells of undetermined significance, HSIL: High-grade squamous intraepithelial lesion, LSIL: Low-grade squamous intraepithelial lesion, AGC-NOS: Atypical glandular cells not otherwise specified, LBC: Liquid-based cytology, CPS: Conventional Pap smear, SCC: Squamous cell carcinoma

spores were appreciable more in CPS smears, whereas Candidal hyphae were clearer on LBC smears. Two cases of herpes were detected on LBC smear.

Screening time was 5 ± 1 min for CPS, whereas it was 3 ± 1 min for LBC smear. In the LBC smear, the time taken was significantly less, which was statistically significant ($P < 0.05$).

Discussion

In our study, a comparison was made between conventional Pap and LBC smears (prepared by Eziprep semiautomated LBC technique which is under Medical Equipment Manufacturing Company, Headquarters – Chennai, India) on the basis of 12 parameters, including smear adequacy, representation (Endocervical cells), inflammatory background, hemorrhagic background, diathetic background, uniform distribution, cell overlapping, presence of artifacts, architectural and cellular morphologic changes, interpretation of results, detection of organisms, and screening time.

The number of unsatisfactory smears in our study was higher in CPS (5%) as compared to LBC (1.4%). This result was similar to most studies including Singh *et al*.,[16] Sherwani *et al*.,[21] and Gupta *et al*.[20] The result was different to study by Sharma *et al*.[17] and Davey *et al*.[22] where there was no discernible difference between LBC and CPS in the percentage of insufficient or poor smears.

The most frequent cause of unsatisfactory smears in CPS is obscuring due to inflammatory cells and hemorrhage. Among LBC, only cellular inadequacy led to unsatisfactory smears. In our study, cellular inadequacy was noted in both techniques almost equally and was due to the faulty technique in obtaining the sample.

Based on the presence or absence of endocervical cells, representation was assessed. More LBC smears (60%) in our research revealed the presence of endocervical cells. This can be due to the LBC smears' clearer background, which made it easier to understand the transformation zone component. The direct transfer of the complete collecting device for the preservation and homogenization of the sample makes LBC more likely to be representative than CPS, which is also frequently linked with the loss of some cells during transfer to slide. Our findings agreed with Sharma *et al*.[17] 's research (50%) and Bergeron and Fagnani.[23] 's study (13%) but not Strander *et al*.[24] 's study, which found that endocervical cells were absent in LBC smears compared to CPS.

The inflammatory background was more common in CPS smears (95%), i.e. more LBC smears showed a clearer background. This result was in accordance with all previous studies including Gupta *et al*.,[20] Sharma *et al*.,[17] Singh *et al*.,[16] Sherwani *et al*.,[21] and Deshou *et al*.[19]

Both the CPS and the LBC have comparable inflammatory cell morphologies. While they were more dispersed in CPS, the neutrophils had higher clumping in LBC smears. According to a research by Sharma *et al*.,[17] this was the case. The ability of the LBC preservation fluid to adhere to the inflammatory cells in LBC smears is what causes clumping. This also explains why LBC smears have a cleaner background. Since neutrophils can still be observed in LBC while being decreased, inflammation is still present.

Haemorrhagic background was more commonly seen in CPS (35%) as opposed to LBC (12.6%), again signifying the clearer background in LBC smears. This result is also in accordance with all previous studies including Gupta *et al*.,[20] Sharma *et al*.,[17] Singh *et al*.,[16] Sherwani *et al*.,[21] and Deshou *et al*.[19]

Diathetic background was noted in two cases of invasive carcinoma and could be visualized equally in both techniques.

While it was seen in (65%) of LBC smears, uniform cell distributions were only detected in 72 (12%) of CPS smears. This outcome agrees with research by Sherwani *et al*.[21] According to a research by Deshou *et al*.,[19] uniform cell distribution occurs more frequently in CPS than LP. This is not the case with our research. Ninety-three percent of CPS preparations showed cellular overlapping, compared to 42% of LBC smears. This result is in concordance with study by Gupta *et al*.[20] which mentions minimal overlapping in LBC smears. In contrast, a study by Deshou *et al*.[19] showed a similar rate of overlapping in both techniques.

The presence of artifacts was noted in almost all (95%) of CPS smears and less of (38%) LBC smears. This is in concordance with all previous studies including Gupta *et al*.,[20] Sharma *et al*.,[17] Singh *et al*.,[16] Sherwani *et al*.,[21] and Deshou *et al*.[19]

Architectural and morphologic changes were seen concordantly in both techniques, i.e. 136 (26%) in CPS and 120 (20%) LBC cases in our study. This correlated with a study of Gupta *et al.*[20] However, in the study by Deshou *et al.*,[19] changes were more commonly seen in CPS smears, and very less in LBC. This contrasted our findings.

Interpretation of cytological diagnoses was found to be concordant with both techniques in our study. In the case of CPS, 85% of cases were reported as NILM, whereas 9.7% of cases were reported as epithelial cell abnormality. In LBC smears, 87.3% were reported as NILM, whereas 11% were reported as epithelial cell abnormality. This result is similar to the study by Gupta *et al.*[20] and Singh *et al.*[16]

According to study by Abulafia *et al.*,[25] Obwegeser *et al.*,[26] Maccallini *et al.*,[27] and Davey *et al.*,[22] although there is no noticeable difference in the detection of low-grade squamous intraepithelial lesion/high-grade squamous intraepithelial lesion (LSIL/HSIL), the interpretation of atypical squamous cells of undetermined significance (ASCUS) is observed in CPS. However, the majority of research asserts that LBC is more effective than CPS at detecting LSIL and HSIL. These authors claim that ASCUS interpretations using LBC do not happen very often. Improvements in ASCUS detection rates using LBC are claimed by Bergeron and Fagnani.[23] and Ilter *et al.*[28] In our research, previously diagnosed two NILM cases letter diagnosed as LSIL on LBC.

CPS revealed high-grade lesions in 93% of the smears in the research by Strander *et al.*[24] as compared to 83% of LBC smears. In our study, 58 cases (or 9.7%) of epithelial cell abnormality on LBC and a total of 66 cases (or 11%) on LBC were found.

ASCUS was seen in 30 (5%) LBC smears, whereas it was seen in 26 (4.3%) CPS smears. Furthermore, atypical squamous cells – cannot exclude HSIL (ASC-H) were detected on LBC smear and it could not be identified on CPS smear. This finding is similar to study by Gupta *et al.*[20] and Singh *et al.*[16] where concordance between the two techniques was similar, in contrast to study by Sharma *et al.*,[17] where LBC was unable to detect ASCUS or ASC-H.

LSIL was seen in 14 (2.3%) smears in LBC, whereas it was seen in 12 (2%) smears in CPS. HSIL was detected in 6 (1%), squamous cell carcinoma in 8 (1.3%), atypical glandular cells – not otherwise specified in 2 (0.3%), and adenocarcinoma in 4 (0.6%) smears in both techniques. This correlates with study by Gupta *et al.*[20] and Singh *et al.*[16] where there was concordance between the two techniques in detecting these abnormalities.

There was no significant difference between CPS and LBC smears in terms of the nonneoplastic reactive changes seen in our study. This is consistent with the research of Sharma *et al.*[17] In our study, the importance of organisms, including commensals and pathogenic species, was better understood in CPS. This correlates with study by Gupta *et al.*[20] and Singh *et al.*[16]

Screening time was considerably reduced in LBC (3 ± 1 min) as compared to CPS (5 ± 1 min) smears. This correlates with almost all studies including Gupta *et al.*,[20] Sharma *et al.*,[17] Singh *et al.*,[16] Sherwani *et al.*,[21] and Deshou *et al.*[19] This is explained by the fact that uniformly thin LBC smears without any obscuring elements were extremely simple to screen for and report.

Conclusion

In our study, we compared a semiautomated LBC technique with conventional Pap assessing the morphological difference between the two smears and its impact on reaching a diagnosis. The advantages of the LBC technique in terms of cleaner background, more uniform distribution, less overlapping of cells, lesser artifacts lead to a considerable decrease in screening time. Furthermore, the number of unsatisfactory smears was comparatively found to be lesser. Moreover, the added advantage of being able to store the sample with enough cells for ancillary testing is the cherry on the cake. However, in terms of cellular morphology, detection of pathological organisms or even coming to the diagnoses in satisfactory CPS smears, there was not much of a difference.

With a clear background, this low-cost LBC technique shows the potential in producing monolayered cervical smears. Although not statistically significant, the detection of low-grade lesions was seen to be improved in the liquid-based smears as compared to traditional smears. Such inexpensive LBC devices should be made more widely available, and their efficacy should be evaluated from several perspectives. The developing nations of the world are where these kinds of low-cost methods need to be deployed since they are most affected by invasive cervical cancers in the modern times.

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Conflicts of interest

There are no conflicts of interest.

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