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Original Research Article

A comparative analysis of conventional smear and sure path liquid-based cytology with cell block preparation

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ABSTRACT

Background: Cervical cancer is ranked as the most frequent cancer in women in India. Conventional papanicolaou smear has been the mainstay of cervical cancer screening since the 1960s. As an alternative liquid-based cytology (LBC) was introduced in the mid-1990s, which are found to increase cytologic detection of squamous intraepithelial lesions and a reduction in the number of unsatisfactory pap tests.
Present study aims at comparison of liquid-based cytology with conventional cytology in detecting uterine cervical intraepithelial lesions.
Methods: The present study was conducted in the department of pathology in collaboration with the department of obstetrics and gynecology, Pt. B.D. Sharma PGIMS Rohtak including 100 non-pregnant female patients coming in the outpatient department of obstetrics and gynecology. Both liquid based and conventional pap smears were examined under the microscope and reported according to the 2001 Bethesda system. Cell blocks were prepared sin all the cases from the residual material of LBC.
Results: Median age was 42 years. More inadequate smears were reported on CS (17%) as compared to LBC (11%). In both, maximum number of cases reported were inflammatory. Equal number of cases were reported as SCC (n=4) in both.
Conclusions: Liquid based cytology has been developed to address the sampling problems of conventional Pap smear. But because of the increased cost of LBC in terms of capital investment, operation and disposables, developing countries should carefully consider the potential benefits and drawbacks of LBC before adopting this new technology.

Keywords: Conventional pap smear, Liquid based cytology, SurePath, Cervical cancer

INTRODUCTION

Carcinoma of the cervix is the second most commonly occurring visceral cancer in women and the third most common cancer-causing death in women (after cancers of the breast and lung). It is the commonest in some parts of the developing world.[1] Worldwide there were estimated 5,30,000 new cases and 2,70,000 deaths annually. Eighty five percent of these deaths occurred in developing countries. Current estimates indicate that every year 96922 women are diagnosed with cervical cancer and 60078 die from the disease. Cervical cancer ranks as the 2nd most frequent cancer among women in India and the 2nd most frequent cancer among women between 15 and 44 years of age.[2] Its epidemiology shows wide geographical variation in its occurrence and these differences are related to social and economic factors as well as to religion, and the influence of these factors on sexual practices.[3] Persistent infection with high-risk human papillomavirus (HPV) particularly types 16 and 18 can also lead to development of cervical cancer.[4]

Average age of patients with invasive cervical cancer is 45 years.[5]

Cervical cancer is ranked as the most frequent cancer in women in India. India has a population of approximately 365.71 million women above 15 years of age, who are at risk of developing cervical cancer.[6] In 2009, time trend analysis of a ten-year data in Bangalore, Bombay and Madras and a four-year data in Delhi did not reveal a statistically significant decrease or increase in the incidence of uterine cervical cancer for most of the age groups.[7] The data on the prevalence of cervical epithelial abnormalities in various population in India is not known, so there is an urgent need for initiation of community screening and educational programs for the control and prevention of cervical cancer in India.[8]

Conventional cytology i.e., the Papanicolaou (pap) smear has been the mainstay of cervical cancer screening since the 1960s and is credited with successfully reducing the incidence and mortality of invasive cervical cancer in many developed countries. Nonetheless, the accuracy of this important screening tool remains controversial, with several large meta-analysis suggesting that both the sensitivity and specificity of cervical cytology is relatively low (30% to 87% sensitivity, 86% to 100% specificity).[9,10]

As an alternative to conventional cytology, liquid based cytology (LBC) was introduced in the mid-1990s. ThinPrep and SurePath are found to increase cytologic detection of squamous intraepithelial lesions and a reduction in the number of unsatisfactory pap tests, compared with the conventional Pap and provide residual cellular material for subsequent molecular testing (e.g., testing for "high risk" types of HPV DNA).[9,11]

SurePath system results in lower rate of unsatisfactory smears as compared to ThinPrep system, dues to different slide processing mechanism, better enrichment process which is able to handle significantly greater amounts of blood or mucus than Thin Prep's membrane filtration process and distinctive sampling devices that prevent loss of cells due to application of pressure and rinsing as seen in ThinPrep.[12]

The rate of colposcopic examinations for repeated unsatisfactory conventional pap smears has also fallen from almost 25% to 0.5%.[13] But liquid based cytology has been questioned and criticism has been raised regarding the design of the studies that proved its superiority.[14,15]

The cell block technique is an important complement to the various methods for cytologic diagnosis of cytologic samples including pap smears. The cell block can retain minute tissue fragments equivalent to micro biopsy, providing architectural insight as well as cytomorphologic details.[16] The main advantage of cell block is the potential to make many sections for special stains and immunohistochemical studies. However, the disadvantages of this technique are increased processing time, decreased cellularity due to singly scattered cells and also there is no well-defined criteria on the specimen adequacy of cell block slides. A new method of cell block preparation using 10% alcohol-formalin as a fixative is a simple, inexpensive method and it does not require any special training or instrument.

HPV is a proven carcinogen for cervical cancers and $p16^{INK4a}$ (p16) is an excellent surrogate marker for HPV-related dysplasia. p16 is a cell-cycle inhibitor that binds to cyclin-dependent kinase 4 (CDK4) and prevents the phosphorylation and subsequent inactivation of the retinoblastoma protein.[17] But the reproducibility of p16 immunostaining was limited in the many studies due to insufficiently standardized interpretation of its immunostaining.

Hence, the present study aims at comparison of liquid-based cytology with conventional cytology in detecting uterine cervical epithelial lesions and immunohistochemical (IHC) expression study on cell blocks prepared from LBC samples from uterine cervix in cases of epithelial malignancies.

METHODS

The present study is an original research article conducted over a period of two years (From December 2014 to December 2016) in department of pathology in collaboration with the department of obstetrics and gynaecology, Pt. B. D. Sharma PGIMS Rohtak. Study has been approved by the ethical committee of the institution.

Study included 100 non-pregnant female patients coming in outpatient department of obstetrics and gynaecology. Informed written consent was taken from all the patients. Conventional pap smear was taken with Ayre's spatula and at the same time, sample for the liquid-based cytology (SurePath) was taken with Rovers Cervex brush. Entire head of the brush was removed and placed in a vial of ethanol based fixative solution. The samples were labelled and transported to the cytology laboratory where they were processed and results of all techniques were correlated with the clinical examination/histopathological examination of the specimen/combined diagnosis taking into consideration all modalities. Suitability of SurePath (LBC) technique for its utilization for cell block preparation and their subsequent uses for IHC (wherever necessary) were also assessed.

Both liquid based and conventional pap smears were examined under the microscope and reported according to the 2001 Bethesda system. Cell blocks were prepared by conventional sedimentation method in all cases from the residual material of LBC. IHC on cell block were analysed in the cases of SIL and SCC. Histopathological correlation was done in cases where available.

Statistical analysis

The whole data was entered in Microsoft excel sheet and analysed using SPSS v20 software. The results obtained were interpreted using chi-square test. The p value was calculated and $p<0.05$ was considered statistically significant.

RESULTS

The patients in the study were in the age group of 0-80 years with the class interval of 20 years. Median age was 42 years. Out of a total of 100 cases, maximum number of cases were in the age group of 41-60 years.

More inadequate smears were reported on conventional smear (CS) (17%) as compared to liquid-based cytology (LBC) (11%) (Figure 1). Endocervical cells seen less on CS.

In both, maximum number of cases reported were inflammatory. Equal number of cases were reported as SCC (n=4) in both. One case of HSIL on CS was reported as LSIL on LBC and one case of inflammatory lesion on CS was reported as LSIL on LBC (Table 1).

No significant difference was seen between CS and LBC method in detecting various lesions like atrophy (p=0.480), inflammatory (p=0.853), atrophy with inflammation (p=0.366), bacterial vaginosis (p=1.0), HSIL (p=0.564), SCC (p=1.0) and the reporting smears as normal (p=0.109) and inadequate (p value of 0.257) (Table 2). Three of squamous cell carcinoma (SCC) cases were in the age group of 21-40 years (75%) and one in the age group of 41-60 years in conventional as well as LBC smears. Also, there was no significant difference observed between HSIL and SCC cases in the age group of 41-60 years (p=0.171) in both (Figure 2).

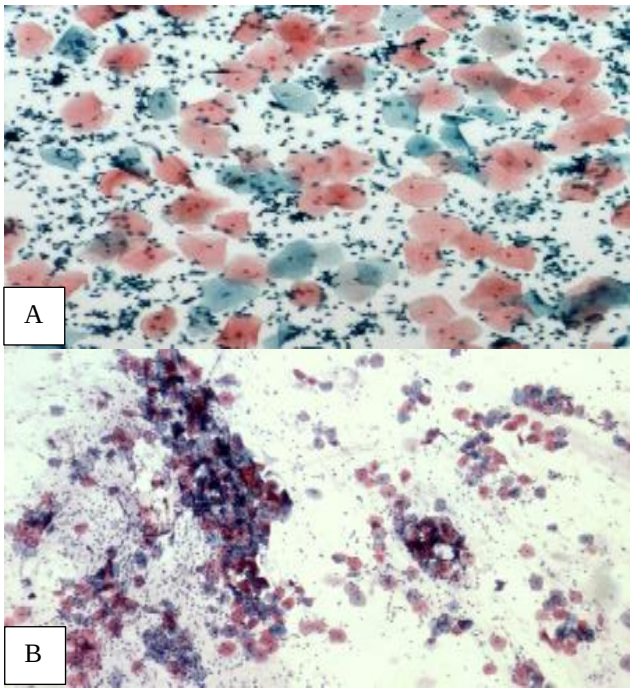

Figure 1 (A and B): Inflammatory change on conventional smear and LBC (Papanicolaou stain 40X and 100X).

Table 1: Comparison between CS, LBC smear and cell block findings.

Findings	CS		LBC		Cell block		P value
	No. of cases (n=100)	Percentage (%)	No. of cases (n=100)	Percentage (%)	No. of cases (n=100)	Percentage (%)	
Benign	94	94	93	93	98	98	0.229
SIL	02	2	03	3	0	0	0.241
SCC	04	4	04	4	02	2	0.661
Total	100	100	100	100	100	100	

Table 2: Comparison of CS and LBC smear in detecting various lesions.

Findings	CS		LBC		P value
	No. of cases (n=100)	Percentage (%)	No. of cases (n=100)	Percentage (%)	
Normal	04	4	10	10	0.109
Atrophy	03	3	05	5	0.480
Inflammatory	57	57	59	59	0.853
Atrophy with inflammation	07	7	04	4	0.366
Bacterial vaginosis	01	1	01	1	1.00
LSIL	0	0	02	2	-
HSIL	02	2	01	1	0.564
SCC	04	4	04	4	1.00
Inadequate	17	17	11	11	0.257
Adequate but no endocervical cells	05	5	03	3	0.480
Total	100	100	100	100	

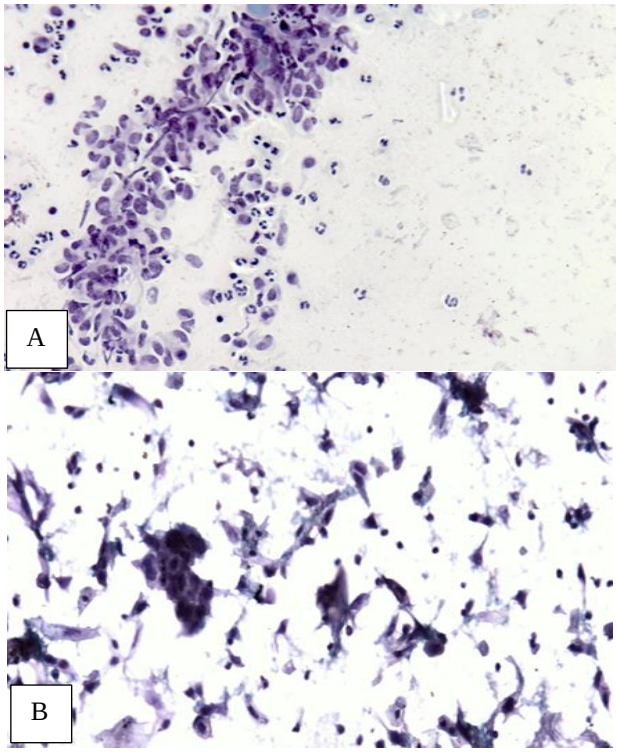

Figure 2: Squamous cell carcinoma on conventional smear (A) and LBC (B) (Pap stain 200X).

Cell blocks prepared from LBC residue showed high cellularity in 42% cases, intermediate in 18% and low in 40% cases.

Cell block detected SCC in two cases only (n=2, 50%) and no SIL lesion identified. Two cases of SCC identified on conventional and LBC smear are found to be inflammatory on cell block. No significant difference was observed between CS, LBC and cell block methods in detecting benign cases (p=0.229), SIL (p=0.241) and SCC (p=0.661).

Immunostaining with $p16^{INK4a}$ on cell blocks prepared from residual material of LBC in one case of HSIL and two cases of SCC was performed. It showed positive staining in only two cases of SCC and negative in a case of HSIL. In the remaining cases of SIL and SCC, material in cell block was insufficient for the marker to be applied.

DISCUSSION

Globally, carcinoma of cervix is the second most frequent cancer in women after breast carcinoma.[18] Detection of cervical premalignant lesions is a crucial component to reduce the associated morbidity and mortality. In underdeveloped countries that have no regular Pap screening programs, 80% of invasive cervical cancer still occurs.[19,20] The Pap smear has been utilized for cervical cancer screening for more than 50 years. Despite being credited with a 70% reduction in mortality for cervical cancer, the false negative rate is still a cause for concern. Several new technologies have recently been introduced like LBC, cell block and HPV testing to decrease the occurrence of false-negative results due to problems with sampling, screening and interpretation.

Present study constitutes 100 cases each of conventional and LBC (SurePath) smears. Both samples were taken from the same patient as in studies by Davey et al, Zhu et al, Afsan et al and Sharma et al.[21-24] Lesser number of patients in our study could be attributed to fewer number of females willing to give both conventional and LBC sample, less awareness among them and also to the limited time period of two years.

We have not found any statistically significant difference in reporting unsatisfactory slides between two methods (p=0.257). Whereas Fremont-Smith et al found a statistically significantly lower proportion of unsatisfactory slides using the SurePath test compared with conventional slides (p=0.00001).[25] Similarly, Beerman et al, Weintraub and Morabia had reported an increased number of satisfactory cases on LBC than conventional smears.[26,27] Also, a greater number of unsatisfactory cases were reported on LBC smears than conventional smears in study by Monsonego et al, Taylor et al and Davey et al.[9,21,28]

The most common cause of unsatisfactory smear in both conventional and LBC smear in our study was obscuring blood (n=09, 52.94% and n=05, 45.45% respectively) followed by obscuring inflammation in conventional smear (n=05, 29.41%) and scant cellularity in LBC smear, similar to the study by Ronco et al whereas, as in the study by Afsan et al, the most common cause of unsatisfactory smear on LBC was scant cellularity in 3 cases (1.9%) and on conventional smear, thick smear was the commonest cause in the same number of cases.[23,29]

In our study, LBC was not found to provide a statistically significant higher detection rate for HSIL (p=0.564) and SCC (p=1.0) compared to conventional slides similar to Beerman et al, who observed that the percentages of LSIL and HSIL lesions and squamous cell carcinoma were similar between the conventional and LBC smears.[26] Similarly Hishhoi et al also did not find any significant differences in detection of lesions on CS and LBC.[30] In contrast to our study, Fremont-Smith et al, observed statistically significant higher detection rate was found for HSIL and LSIL (p<0.00001 for each lesion) compared with conventional slides.[25] Similar finding were seen in studies conducted by Afsan et al, who found detection rate of LSIL increased from 10.6% to 18.1% (p<0.05) with LBC than with conventional pap and detection of HSIL increased from 0.6% to 4.3% (p<0.05) and Atif et al found that squamous epithelial lesion detection rate was higher using LBC than CS.[23,31] Also, I Kiyoshi et al have conducted one of the largest study comprising total of 3 815 131 women revealed that compared to conventional cytology, the detection rates with liquid-based cytology were significantly higher

(1.42 times) for CIN1+ and CIN2+.[32] Positive predictive value ratios of CIN1+ and CIN2+ were also significantly higher for liquid-based cytology than for conventional cytology. However, there was no significant difference between liquid-based cytology and conventional cytology for detection rates and positive predictive values of CIN3+ and cancer. The rate of unsatisfactory specimens was significantly lower with liquid-based cytology compared to conventional cytology.[32]

Study of 29 cases by Afsan et al, diagnosed as LSIL on LBC, 2 cases had normal histology, 1 case had moderate dysplasia and 26 cases had mild dysplastic changes on histopathology whereas, all the 6 cases of carcinoma on LBC revealed squamous cell carcinoma on histopathology.[23] Similarly in our study out of two HSIL cases diagnosed on conventional smear, one was found to be LSIL on LBC (histology not available), other case of HSIL diagnosed on both conventional and LBC was diagnosed as chronic cervicitis on histology whereas, four cases were of SCC on both methods. Histology was not available in two of SCC cases and other two cases were diagnosed as SCC on histology. Study done by Fremont-Smith et al, showed that the percentage of slides for which the pap smear and the biopsy results for HSIL were found to correlate among biopsy specimens was not found to be statistically significantly different at three different sites ($p=0.91$, $p=1.00$, $p=1.00$).[24]

An adequate cell block slide was defined as one that contained at least 10 intermediate power fields (20X) of cellular elements. Adequate cellularity can be divided into 3 categories on the basis of cellularity on a 20X field (high cellularity: >50% cellular components, intermediate cellularity: 25% to 50% cellular components and low cellularity: <25% cellular components).[33] In our study, 42% of cell blocks were of high cellularity, 40% were of intermediate and 18% were of low cellularity in contrast to the study by Liu et al in which only 10% cases were of low cellularity.[34] It could be attributed to the difference in the method applied for cell block preparation. Simple sedimentation method was used in our study whereas plasma thrombin method was used in the study by Liu et al.[34] A study by Diaz-Rosario and Kabawat showed that adequate cellularity from cell blocks was obtained in 75 out of 95 cases (79%).[35]

Cases that are suspicious or equivocal on the smears can be diagnosed definitively with the aid of a cell block preparation. In some cases, smears are diagnostic when the cell block is not. Therefore, the best cytologic evaluation combines the use of both smears and the cell block. The correlation between SurePath and the cell block prepared depend on the amount of residual material left for making cell block. The range of correlation between the ThinPrep and the cell block prepared from the same vial is dependent on the number of cells (normal and abnormal) originally collected and on the fact that the ThinPrep was prepared initially and the cell block was prepared from what remained after the dispersal of the specimen within the vial.

In our study, out of 100 cell blocks, two were interpreted as SCC which correlate with the conventional and LBC findings. Remaining cases were within normal limits (WNL). A study by Akpolat et al found good correlation (73%) between cell block diagnosis and ThinPrep (LBC) diagnosis.[36] Keyhani-Rofagha et al studied 125 cell blocks, 15 were interpreted as HSIL (On Thin-Prep 11 were reported as HSIL and 4 were reported as LSIL), 70 were interpreted as LSIL (On ThinPrep 55 were reported as LSIL, 10 as HSIL and 5 as ASCUS), 24 were interpreted as ASCUS (On Thin-Prep 6 cases were reported as ASCUS, 16 as LSIL, 1 as HSIL and 1 case being WNL) and 16 were considered to be WNL.[35] Also, only a limited number of reports in the literature delineate the utility of a cell block prepared from a liquid-based cytologic smear in the diagnosis of cervical squamous cell lesions.[27]

In our study, out of 4 cases of SCC, 2 cases showed positive immunostaining for p16. One case of HSIL was negative for p16 immunostaining. In the study by Shidham et al, 21 out of 28 HSsIL cases were p16 positive.[37] Biopsies were available in 11 out of 28 cases and 92% of biopsies were positive for CIN I and above. In the study by Liu et al, one case of biopsy-proven LSIL had positive p16 staining and six false-positive cases were noted.[34] In study by Sakamoto et al a case of cervical LBC sample that was not clinically suspected of malignancy showed HSIL on cell block.[38] These cells were immunohistochemically positive for Ki-67 in their nuclei, β-catenin in their cell membrane and cytoplasm and p16 in their nuclei as well as cytoplasm.

It is also debatable whether pap smear or cervical biopsy should serve as the gold standard. Still cell block sections from residual SurePath or ThinPrep samples are helpful with certain problematic cases such as metastatic tumor of unknown origin.

The present study concluded that use of this technique has the potential to decrease the number of slides screened per case and decrease the turn-around-time. It is easier and less time consuming to screen and interpret LBC smears as the cells are limited to smaller areas and background blood-debris is cleared. The residual sample can be kept at room temperature for 4 weeks, without compromising the cell preservation or quality of slide preparation. Further, immunocytochemistry and molecular studies, such as the detection of hrHPV can be performed on LBC slides which is a major advantage of LBC avoiding need for surgical biopsy required for choosing appropriate therapy in carcinoma cases. Also, LBC is cost-effective in mass cervical cancer screening.

To the best of our knowledge, well-defined criteria on the specimen adequacy of cell block slides are not available. There is no consensus on how many cells a cell block

slide should contain to be labelled as an adequate sample. This also depends on the type of LBC method used for preparing cell block. Our study used residual material from SurePath cytologic samples.

CONCLUSION

Liquid based cytology has been developed to address the sampling problems of conventional pap smear and can improve the quality of the sample leading to early detection and treatment of uterine cervical lesions. Thus, our study was conducted to compare conventional with liquid based cytology and it was found that no single method is sufficient enough for definite diagnosis, however LBC adds as an adjunct to conventional cytology for definite diagnosis. But because of the increased cost of LBC in terms of capital investment, operation and disposables, developing countries should carefully consider the potential benefits and drawbacks of LBC before adopting this new technology. Further studies with number and wider spectrum of uterine cervical lesions are required if LBC is the first and the only methodology applied.

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