Original Article

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Comparison of Manual Liquid Based Cytology and Conventional Pap Smear in Cervical Cancer Screening

Pathology Section

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ABSTRACT

Introduction: Pap smear is a screening procedure to detect precancerous lesions to prevent subsequent invasive cervical cancer. Manual Liquid Based Cytology (MLBC) has been developed as an alternative to Conventional Pap Smear (CPS) as it is said to increase the rate of detection of precancerous lesions as it reduces the screening time, the artifacts, giving a clean background on the smear and providing residual cellular material for molecular testing (HPV DNA).

Aim: To compare the diagnostic performance of manual liquid based cytology and conventional Pap smear in cervical cancer screening.

Materials and Methods: This is a prospective study, done for a period of 2 months, in 97 women with CPS and MLBC and compared with the gold standard- histopathology. The smears were stained by Rapid Pap stain and reported using Bethesda system of reporting.

Results: MLBC showed a higher satisfactory rate of 88.7% and CPS 86.6%. MLBC showed clean background in 34% while CPS only in 8%. The sensitivity and specificity of CPS was 33.33% and 95.65%. The sensitivity and specificity of MLBC was 22.22% and 95.65%. The p-value was not significant (>0.05).

Conclusion: MLBC was better than CPS only with respect to specimen adequacy and clean background. Since, LBC is new technique, training in sample collection, processing and analyzing the MLBC slides may improve the efficiency of this method in low resource setting.

Keywords: Cervical cytology, Clean background, Low resource setting

INTRODUCTION

Cervical cancer is the second most common cancer in women in India [1]. Cervical cancer is preceded by squamous intraepithelial lesions which can be detected before it transforms to invasive cancer. This forms the basis of the cytological screening [2,3]. Pap smear has been the mainstay of cervical cancer screening and has a major impact on the morbidity and mortality from cervical cancer [4].

The false negative rates of Pap smear range from 6-50% [5] and many meta-analyses suggests that both the sensitivity and specificity of cervical cytology is low [6]. Sampling has improved with new collection devices which collect larger cervical samples, and transfer the sample into the liquid preservative before processing, called as Liquid Based Cytology (LBC) [7-9]. LBC has advantages over CPS and provides residual material for molecular testing (HPV DNA) [9-13].

There is a lack of quality studies to compare the test performance of LBC and CPS. Therefore, this study aims at comparing CPS and MLBC.

MATERIALS AND METHODS

This is a prospective study done for a period of 2 months in 97 women attending the OBG OPD in a Tertiary Hospital setting in Bengaluru, India, 2012 for screening of cervical cancer with CPS technique and MLBC. The samples were compared with the gold standard- histopathological sections (from colposcopic biopsies and cervical specimens from hysterectomy) wherever available. An informed written consent to participate in the study was taken from all the women. There was no financial burden on the subjects. The study protocol was approved by the Institutional Review Board and Ethical clearance was given.

Rationale for Sample Size

A study carried out on comparing CPS with LBC for detection of precancerous lesions and cervical cancer has revealed the sensitivity of liquid based cytology to be 97.6% as compared to 53.7% for CPS [13]. Based on the above findings, with a power of the study at 90% and alpha error of 1% it was estimated nearly 30 subjects to be studied. However, to analyze the results according to the various grades and age of women, it was proposed to include 97 women in the study.

Inclusion Criteria

The cervical specimens of the following patients are included in the study.

a) Age group: 20-70 years

b) Previously unscreened women

Exclusion Criteria

a) Pregnant women

b) Women with history of prior treatment for cervical intraepithelial neoplasia or cervical cancer.

Procedure

In each woman who was screened, the conventional Pap smear was obtained with Cyto brush and Ayre's spatula respectively. The exfoliated cells collected on the brush and spatula were smeared on to two separate glass slides and was immediately fixed with 95% ethyl alcohol.

In the same woman, rovers cervex brush was used to collect the exfoliated cells for MLBC. The head of the cervex brush was detached and placed in the liquid prep collection vial containing specific preservative solution and specimen processed in the laboratory. Specimen collected in vials are shaken vigorously and poured into centrifuge tube containing 4 ml cleaning solution and centrifuged at 3000 rpm for 10 minutes. To the residual pellet 500 µl of cellular base was added and vortex mixed. 50 µl of sample is pipetted on to a slide, smeared, dried and stained with rapid Pap. The specimen could be stored in the vial for a period of up to 90 days from the time of collection. Cytology was reported using the Bethesda system of reporting. All the smears of MLBC and CPS were evaluated by the same pathologist and was blinded for matched CPS and MLBC and histopathology slides.

STATISTICAL ANALYSIS

All the qualitative data was summarised in terms of percentages. Quantitative data such as age, parity etc., was described through descriptive statistics such as mean, standard deviation. Comparison of the two diagnostic procedures was carried out by calculating the sensitivity, specificity, positive and negative predictive values. The differences in the proportions for the various categories of diagnosis such as normal, LSIL, HSIL, carcinoma between the two screening methods was statistically assessed through Chi square test of significance. A p-value ≤ 0.05 was considered for statistical significance.

RESULTS

The study was done in 97 women who underwent CPS and MLBC. Histopathological analysis was done in 41 cases out of 97(42.3%).

Data was analysed using SPSS version 17. Sensitivity, specificity, PPV and NPV were estimated considering biopsy (histopathology) as the gold standard.

The mean age observed was 41 years (range was 20-70 years)

Out of 97 women who were screened 56 women (57.7%) complained of white discharge which was the major presenting complaint in those screened.

Specimen Adequacy

The CPS was satisfactory for evaluation in 84 cases while MLBC was satisfactory in 86 cases. Thus, the adequacy rate was slightly higher in MLBC (88.7%) than CPS (86.6%) [Table/Fig-1].

Endocervical cells and metaplastic cells were more in CPS than in MLBC as shown in [Table/Fig-2].

Cellularity

The cellularity was almost the same in both the methods with superficial, intermediate and parabasal cells being the most common type of cells seen in the smears [Table/Fig- 2].

	CPS	MLBC
Satisfactory	84 (86.6%)	86 (88.7%)
Unsatifactory	13 (13.4%)	11 (11.3%)
Total	97	97

[Table/Fig-1]: Comparison of the specimen adequacy rates.

	CPS	MLBC
Slides with Endocervical Cells	62 (63.9%)	42 (43.4%)
Slides with Metplastic Cells	46 (47.42%)	15 (15.5%)

[Table/Fig-2]: Cellularity and metaplastic cells.

Background

CPS showed the clear background only in 8(8.2%) cases while MLBC showed clean background in 33(34%). Also the cells were not well spread on CPS while the MLBC showed a single layer of uniformly distributed cells [Table/Fig-3].

Background	Conventional Pap Smear (No. of Cases)	Liquid based Cytology (No. of Cases)
Clear	8 (8.2%)	33 (34%)
Inflammatory	66 (68.04%)	61 (62.9%)
Haemorrhagic	4 (4.1%)	1 (1.03%)
Dirty necrotic	1 (1.03%)	1 (1.03%)
Others (mucus, debris)	18 (18.6%)	1 (1.03%)
Total	97	97

[Table/Fig-3]: Comparison of the smear background.

[Table/Fig-4] depicts the spectrum of cases seen on CPS and MLBC.

Out of 97 cases, correlation with histopathology was possible

Diagnosis	CPS	MLBC
Normal	28 (28.9%)	40 (41.2%)
Normal with infection	57 (58.8%)	48 (49.5%)
ASCUS-H	0	3 (3.1%)
LSIL	4 (4.1%)	2 (2.06%)
HSIL	3 (3.1%)	2 (2.06%)
Squamous cell carcinoma	5 (5.1%)	2 (2.06%)
Bacterial vaginosis	6 (6.2%)	26 (26.8%)
Candidiasis	2 (2.06%)	2 (2.06%)
HPV (koilocytic atypia)	0	2 (2.06%)
Trichomonas vaginalis (BB shots)	1 (1.03%)	2 (2.06%)

[Table/Fig-4]: Comparison of the general diagnosis.

in 41 cases. Total 13 cases were diagnosed as precancerous lesions and 5 cases as invasive cancer on histopathology. Twenty one cases were reported to be chronic non specific cervicitis and biopsy was inadequate in 2 cases.

Coccobacilli, clue cells, *Candida* and BB shots with *Trichomonas* infection was seen in CPS and MLBC in varying degrees as show in [Table/Fig-4].

On the whole, the sensitivity and specificity of CPS was 33.33% and 95.65%.The sensitivity and specificity of MLBC was 22.22% and 95.65%.

The PPV for CPS and MLBC were same, that is, 0.8571. The NPV for CPS and MLBC were 0.647and 0.61 respectively [Table/Fig-5]. The p-value was not significant (>0.05).

	CPS	MLBC	p-value
Sensitivity	33.33%	22.22%	NS*
Specificity	95.65%	95.65%	NS*
Positive Predictive Value (+PV)	85.7%	85.7%	NS*
Negative Predictive Value (-PV)	64.7%	61%	NS*

[Table/Fig-5]: Comparison of diagnostic performance of CPS and MLBC.
(*NS- Not significant p value >0.05)

DISCUSSION

LBC is a technique which enables the cells to be suspended in a monolayer and thus improves the detection of precursor lesions by improving the specimen adequacy. It increases the histologically confirmed neoplastic and preneoplastic disease detection and thus improves the effectiveness of cervical cancer screening and also decreases the over diagnosis of the benign processes [2]. Controversy about its diagnostic accuracy prevails inspite of numerous studies and systematic reviews. MLBC is a cost effective method in low resource setting, which can be used as alternative method to much more expensive automated LBC [3].

This is a prospective study of comparison between MLBC and CPS in screening of cervical cancer with histopathological confirmation wherever possible. The study was done in 97 women by both CPS and MLBC technique and histopathological correlation in 41 cases. The mean age in this study was 41 years while the studies Behtash N et al., [5] and Taylor S et al., [6] reported the mean age to be 39 years and 38 years respectively.

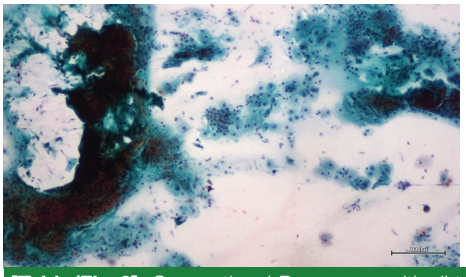
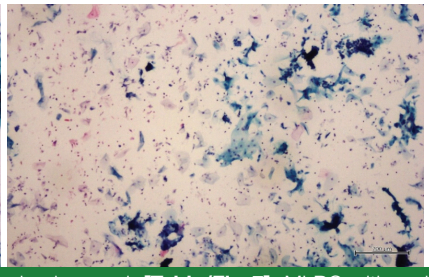
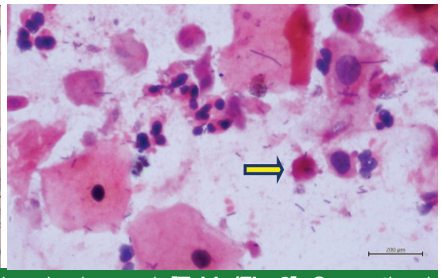
In our study, most of the women, complained of white discharge followed by bleeding per vagina, pain abdomen, dysmenorrhea, dyspareunia, genital ulcers. These are some of the most common complaints in patients with carcinoma cervix [14].

In this study, the specimen adequacy was found to be better with MLBC than CPS with 11 unsatisfactory smears in LBC and 13 in CPS. Many studies have reported LBC is better in terms of specimen adequacy to CPS. Majority of studies comparing LBC and CPS found that quality of slides improved in LBC [15-22], which is consistent with the results obtained in our study that MLBC has higher satisfactory specimen rates as compared to CPS.

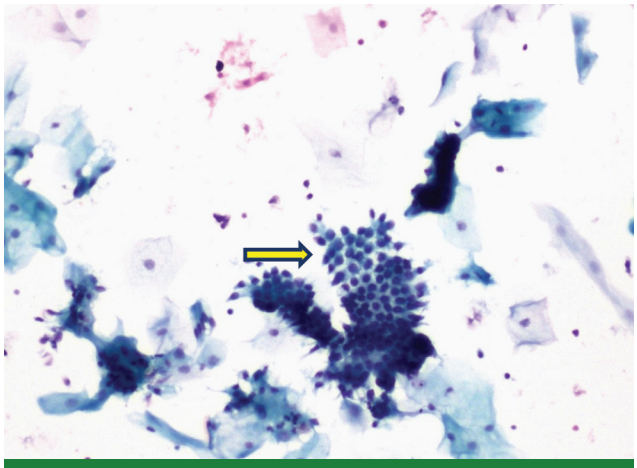
In CPS, specimen adequacy was lesser due to the presence of obscuring blood, inflammation and dirty background [Table/Fig-6] which mask the epithelial cells thus affecting the screening process. Also, in CPS only 20% of the cells collected on the brush are smeared on to the slide leading to lesser cells being transferred to the smear for screening [2].

In MLBC, the background was clear [Table/Fig-7] in most of the smears with uniform distribution of the cells in single layer thus increasing the satisfactory results. This was also due to the fact that the entire specimen collected from the cervix with the rover cervex brush was transferred to the vial for processing without any wastage.

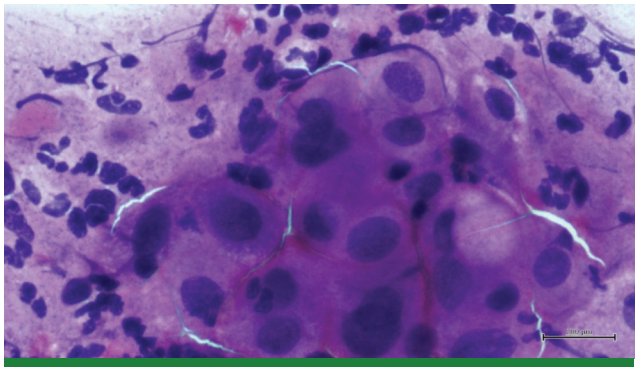
Some studies have reported that the LBC was unsatisfactory

[Table/Fig-6]: Conventional Pap smear with dirty background. **[Table/Fig-7]:** MLBC with a clean background. **[Table/Fig-8]:** Conventional Pap smear with *Trichomonas vaginalis* infection (Indicated by arrow).



[Table/Fig-9]: MLBC with endocervical cells (indicated by arrow).



[Table/Fig-10]: HSIL on conventional Pap smear.

as compared to CPS.

The probable reasons for scant cellularity in few MLBC slides could be technical problems during sample collection, transfer of cells to the slide from the sampling device, deficiencies during processing of the slide, subjective assessment and imprecise use of criteria by the cytologist [21].

Many studies have followed the split sample protocol where one half of the cervical sample collected on the brush was smeared on the slide and the other half was rinsed in the preservative vial. This might have affected the adequacy rates possibly decreasing them in few studies [11-16].

However, in our study the direct to vial method of sample collection was followed similar to few other studies [21, 23].

The MLBC slides that were screened in our study presented with a clean background in 34% devoid of obscuring inflammation, blood and mucus thus improving the screening process. While CPS reported only 8% of slides with clean background.

In MLBC, the cells were uniformly dispersed by a membrane from a suspension of cells in a solution. In CPS, even with excellent collection and sampling techniques, only 20% of the cells were transferred on to the slide from the brush, leading to decreased adequacy and thus imperfect sensitivity and specificity. LBC gives a higher diagnostic yield than conventional cervical smears with proper training as shown in many studies [2,13].

The coccobacilli and clue cells were better detected on MLBC than with CPS. Clue cells which are indicative of bacterial vaginosis were observed in 26 cases in MLBC but only in 6 cases of CPS. Candida was equally detected in both methods but *Trichomonas vaginalis* (BB shots)- [Table/Fig-8] were detected in 2 cases of MLBC as compared to 1 case of CPS. Koilocytic atypia seen with HPV infection was better seen in MLBC [2,13].

It has been reported in earlier studies that endocervical cells were detected less frequently with LBC than with CPS. [11,16]. This may be due to the choice of sampling devices. In our study, the percentage of slides lacking the endocervical cells were 56.7% on MLBC compared to 36.1% on CPS. Thus, CPS had higher detection rates of endocervical cells [Table/Fig-9] than that with MLBC.

In our study MLBC was comparable to CPS on some parameters and superior on few others. Biopsy was done in 41 cases out of which 13 were precancerous lesions reported as CIN1,2,3 and 5 were squamous cell carcinoma. On MLBC, 4 were precancerous and 3 were detected as cancerous whereas in Pap smear, 7 were precancerous (LSIL, HSIL)- [Table/Fig-10] and 5 were cancerous. The results of the current study suggest that the MLBC test may not be superior to the conventional Pap smear in the detection of cervical disease, particularly invasive cervical carcinoma and similar results were reported by Chacho MS et al., [8].

The current study reports higher rate of ASCUS detection in MLBC compared to CPS. ASCUS was reported on 3 slides of MLBC while there was none reported on CPS. This corresponds to a few studies where the ASCUS detection was more with LBC than with CPS [3,11,16,23].

The sensitivity and specificity of CPS was 33.3% and 95.65% respectively while that of MLBC was 22.2% and 95.65% respectively. Though the specificity was the same for both the sensitivity of MLBC was found to be lesser than CPS but the overall sensitivity of both the screening methods was much lower and consistent with a study which has reported the sensitivity of CPS to be varying from 30% to 87% [6].

Our results on sensitivity and specificity are similar to those obtained in other studies where the sensitivity of LBC is lower than that of CPS [6,11,24].

Availability of histopathological biopsies for the precursor lesions which are detected by CPS and MLBC methods, help in better calculation of sensitivity and specificity. The sensitivity of LBC and CPS was higher in few studies [25,26].

While it was almost the same and comparable in few studies [23,27].

In our study p-value was not significant indicating that both the methods of screening are comparable and neither method is superior to the other.

Inadequate sampling, inadequate transfer of sample on to the glass slide or microscopic assessment of the slide may result in false negatives in CPS [2].

False negatives in LBC may be due to sampling errors (not in the control of the laboratory), transfer error (taken care of by the automated LBC technique), detection error or screening error (abnormal cells present but not detected), interpretation error (abnormal cells are detected but not interpreted correctly). Release of cellular material from the collection device may be adversely affected by the cellular mucoid sample and preservative interaction which impacts the final preparation. Special training and attention to details are required to overcome these problems as the cells of LBC are much smaller because of rinsing in the liquid before placing on the slide [8].

LBC is also specific to the lab, equipments, fixatives and polymer solutions [2].

The PPV for MLBC (0.8) was slightly lower than that for CPS (0.8571). This result is same as that obtained by other studies [23].

A few studies have followed the MLBC method of sample preparation [2,3,5,7] while a few others have followed automated LBC [15,16,21,24]. The automated methods reduce the chances of sampling and processing errors. Thus higher rates of sensitivity for LBC were detected on automated methods than manual method. We however followed the manual method of LBC and found lower sensitivity for MLBC than CPS. MLBC is an inexpensive, cost effective method of LBC which we have used to compare with CPS.

In addition, another possible explanation for this difference in performance may be the relative lack of experience of those involved in the collection and interpretation of LBC specimens compared with the CPS. The current study reflects a laboratory's experience with a new technology during the early years of its implementation.

CPS demonstrated a tendency to be more accurate when histopathology was used as the gold standard. Approximately 93% of high-grade readings in Pap smears corresponded with high-grade lesions in histopathology compared with 83% for MLBC. LBC detected lesions to a greater extent, with cytology, were classified as low grade but, with histopathology, were classified as high grade and thus it showed a better detection rate of high grade lesions in histopathology in our study. This hereby stresses the necessity of correct evaluation of cytologic low-grade lesions and leads to the practice of accepting only a second smear as follow-up being questioned [16].

Detection and removal of histologically confirmed, high-grade lesions are the main objectives of cervical screening programs. Histopathology was not done in all the women in our study due to unavoidable practical and ethical reasons, which led to a possibility of verification bias, which however appeared to be insignificant in the study because the proportions of follow-up in histopathology were quite equal between the two methods.

The current study results confirm the lack of increased sensitivity of MLBC compared with conventional cytology. MLBC methods add to the cost of a standard Pap smear. However, liquid-based methods have improved the specimen adequacy, reduced the rate of unsatisfactory smears and increased the detection of epithelial abnormalities which has thus improved the quality of screening as reported by many studies [3].

The precision of sensitivity estimation and our ability to rule out random chance as a possible explanation for the observed difference was limited by the relatively small number of women with high grade disease in our study. Also the sensitivity of both the methods was possibly lower because the number of cases where histopathology was available was only 41 out of 97 cases thus giving us only 41 cases to compare the sensitivity of both the methods.

CONCLUSION

The MLBC and CPS methods were comparable. However the advantages of MLBC include preservation of specimen for ancillary studies, better morphology and research opportunities. Thus, it is worthwhile to study MLBC further as a cost-effective alternative to the automated methods like ThinPrep/SurePath in low resource settings.

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