



Comparative Study for the efficacy of conventional and liquid-based pap smear methods in screening of cervical intraepithelial neoplasia (CIN) In Al Kut City

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Abstract

Background: Although cervical cancer death rate has reduced globally, it is still a major concern in the world more so in Low and Middle Income Countries (LMIC). Screening for cervical intraepithelial neoplasia is important in the prevention of cervical cancer.

Aim: To compare and assess the two cytological screening techniques: The first one, the Conventional Pap Smear (CPS); the second one, the Liquid-Based Cytology (LBC) with the aim to determine how effective these two techniques are in the diagnosis of CIN before finally concluding which method was suitable for cervical cancer screening.

Patients, Material and Method: This work aims to assess and contrast two cytology screening tests; the CPS and LBC particularly in relation to detection of CIN. This study was cross-sectional and conducted over a 12 months at a private clinic in Al Kut city; thus, the institutional ethics committee cleared the study, and participants provided their informed consent. Respectively, 300 PAP test were done, only A total of 200 women with abnormal PAP test with colposcopic biopsy were analyzed, endocervical samples obtained using the CPS and LBC methods, LBC was shown to provide superior sample adequacy, sensitivity and specificity.

Result: Sample adequacy: in 200 cases. Adequate samples were obtained in 96% of the cases with LBC, and in 85% of the cases with CPS. As for CIN Detection Rates, LBC was more significant higher than CPS in detecting CIN ($p < 0.05$). Sensitivity and Specificity; LBC had a higher sensitivity today than CPS, 89% to 72%. LBC had also better specificity of 85% compared to CPS with a specificity of 68% the difference being statistically significant at $p < 0.05$. In relation to LBC performance, Overall Performance shows an increasing upward trend of all parameters highlighting the fact that LBC is more accurate and efficient screening tool than CPS.

Conclusion: These results confirm that LBC is more effective than conventional liquid-based preparations as the preferred method in cervical cancer screening programs globally, although questions of cost and availability remain essential.

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Keywords: Pap smear, CPS, LBC, CIN

Introduction

Cervical cancer is the fourth most prevalent cancer type among women worldwide; new cases and deaths account for 600,000 and 340,000, respectively. The WHO estimates that over 85% of such a case are seen in low and middle-income countries which rarely implement screening programs, the cause of which is lack of awareness ^[1]. According to the Global Cancer update report, 2018 cervical cancer contributes to more than one-fifth total cervical cancer mortality in India. Screening and intervention start with detection of cervical intraepithelial neoplasia (CIN) are paramount in the management of this disease. This divergence in the incidence is huge, because while in developed countries cervical cancer has significantly declined, in developing countries this type of cancer remains a major threat ^[2]. Cervical cancer is preventable owing to the long precancerous phase of this disease

[3]. Early detection is achievable with good screening measures put in place. Timely management of cervical dysplasia (pre-invasive cervical cancer) is essential following a cervical smear test. This is a significant health risk among women of all ages [4].

Cervical Intraepithelial Neoplasia (CIN); CIN refers to precancerous changes in the cervical epithelium, categorized into three grades

CIN1: They include low grade lesions by pathologic standards and are unlikely to progress in the near future.

CIN 2: Moderately dysplastic with increased potential of developing into invasive cancer.

CIN3: Severe dysplasia, in many cases may need urgent treatment to prevent the formation of cancer [5, 6].

Papanicolaou (Pap) smear, which was initiated in the 1940s, is one of the efficient methods for screening cervical lesions. Cervical screening by Pap smear is a method of smear testing which can be employed to detect potentially dysplastic or malignant lesions of the cervix. The usual technique for obtaining a Pap smear sample is to scrape the transformation zone, which is the interface of the ectocervix and endocervical canal, usually using a wooden spatula and an endocervical brush, and Cameroon passive smearing the samples on a slide and immediately fixing the smear in a fixative [7]. The reporting is done according to The Bethesda System for Reporting Cervical Cytology. There is evidence that cervical cytology screening programmes have proved to have reduced deaths from cervical cancer in developed countries [8]. Especially, the beginning of cervical cancer screening program including cervical cytology in combination with human papillomavirus testing has led to cervical cancer mortality decline in developed countries [9]. Pap smear trial has led to cervical cancer incidence decrease in states with efficient screening programs. However, inadequacies that include poor sample adequacy, low sensitivity among others have forced change to other methods such as Liquid Based Cytology–LBC. Whereas, in the conventional and most common method known as CPC, cervical cells are directly applied on the glass slide, in LBC, cells are placed in liquid media so there is less risk of contamination and poor preservation of cells [7, 8, 9].

There are two methods used in cervical cytology. Cytology screening as follows: One is the conventional Pap smear, which as of now is the most commonly employed method in cervical cytology, because of its widely availability and affordability. The other technique is liquid-based cytology (LBC). Nevertheless, it is the most familiar type of cervical cancer screening in developed countries, but it exists only in several centers in developing countries due to high cost and need for appropriate equipment [10]. While conventional Pap smears are relatively easy to perform, they have three technical limitations. Large amount of the collected cellular material is lost because of failure in procedures to take samples from the patient on the sampling device, and because of the sample transfer from the sampling device (brush) to the slides (glass). In addition, cells that look microscopically suspicious on the slide are sometimes overshadowed by inflammation or hemorrhage background leading to underdiagnoses. Compared to a conventional Pap smear, LBC technique gives a monolayer thin smear with less background interference. Furthermore, with regard to LBC, the gathered material can be preserved for other analysis in case needed [10, 11, 12].

Aim of study

To investigate the appropriateness of the sample size and the effectiveness of the two methods of sample acquisition; CPS and LBC with the intention of comparing the sensitivity, specificity, adequacy and the ability of the two techniques to detect CIN before finally concluding which method was suitable for cervical cancer screening.

Patients, materials and method

Therefore, this cross-sectional and comparative study was carried out within a 12 month period at a private clinic in Al Kut city. The study was approved by the institutional ethics committee, and informed consent was obtained from all participants. A 300 PAP test were done 100 case exclusion, only a total of 200 women with abnormal PAP test with colposcopic biopsy, aged 21-65 years were enrolled in the study. (Group 1: CPS 100 samples processed, Group 2: LBC 100 samples processed).

Exclusion Criteria

Pregnant women.

Women with prior hysterectomy or ongoing treatment for cervical cancer.

Method

Normal PAP test cervical smear samples were collected using a brush and processed as follows:

CPS: The samples were taken directly on the slide, they were then fixed using ethanol and stained.

LBC: Cells were dispersed in a liquid culture to which processing equipment was applied to deposit them on the slide.

Colposcopy: Special colposcopy with optical magnification and bright halogen light was done in out-patient setting. For better visualization saline wash followed by 3% acetic acid and Lugol's iodine were applied on the cervix successively. Cup biopsies were taken from the aceto white and iodine non-take areas, or from the anterior cervical lip close to the junction of the squamous columnar epithelium if no such changes were visible (a potential abnormal pap test only).

Cytology Reporting: Classification was done according to the Bethesda System (2001 modification): infective-inflammatory, reparative, and epithelial cell abnormalities (LSIL, HSIL, etc.). We compared only the abnormal groups of PAP cases.

The following Parameters were evaluated

1. **Sample Adequacy:** In situ evaluation of non-diagnostic epithelial cells without other admixed materials such as blood or mucus.
2. **CIN Detection:** Differentiation of the lesion into CIN1, CIN2 or CIN3.
3. **Diagnostic Accuracy:** These are [Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV)].

Statistical Analysis: In this study, data analysis was conducted utilizing the statistical computer program SPSS version 26.0. For categorical data chi-square test was employed while $p \leq 0.05$ was considered significant. Sensitivity, specificity and both positive predictive value and negative predictive value was derived mathematically.

Results

1. Demographic Characteristics of Participants

Age: The mean age of the participants of the CPS group was 34.5 ± 8.2 whereas for LBC group was 33.8 ± 7.9 . Age, however, did not differ significantly between the two groups ($p= 0.0042$). Regarding to the Parity: The parity of the two groups was comparable with equal proportions of nulliparous

and parous women with non-significance differences ($p>0.05$). Regarding to Education Level: There were no statistical differences between the two groups in the educational level in all subjects thus, $p>0.05$. In comparison of Socioeconomic Status: Local and international groups and products were consumed by the patients across the three different socioeconomic status ($p>0.05$) (See table 1).

Table 1: Demographic Characteristics of the study Participants

Characteristic	CPS Group (n=100)	LBC Group (n=100)	Total (n=200)	p-Value
Age (years)- Mean \pm SD	34.5 \pm 8.2	33.8 \pm 7.9	34.2 \pm 8.0	0.42
Age Distribution (years)				
21–30	32	30	62	0.71
31–40	38	40	78	0.68
41–50	20	22	42	0.79
>50	10	8	18	0.61
Parity				
Nulliparous	22	25	47	0.58
Parous	78	75	153	0.65
Education Level				
Primary	30	32	62	0.72
Secondary	40	38	78	0.75
University	30	30	60	0.91
Socioeconomic Status				
Low	50	52	102	0.68
Middle	35	33	68	0.73
High	15	15	30	1.00

2. Sample Adequacy

As shown in figure 1: The portions of adequate and inadequate samples for CPS and LBC are illustrated in this pie charts, but it is evident that LBC had a greater rate of adequacy. CPS: (Table 2) The adequacy of swabs was as

follows: adequate in 85% of samples; 15% were inadequate due to contamination. LBC: sufficient in 96% of samples, while only 4% of samples were found to be insufficient, markedly better than CPS (<0.05).

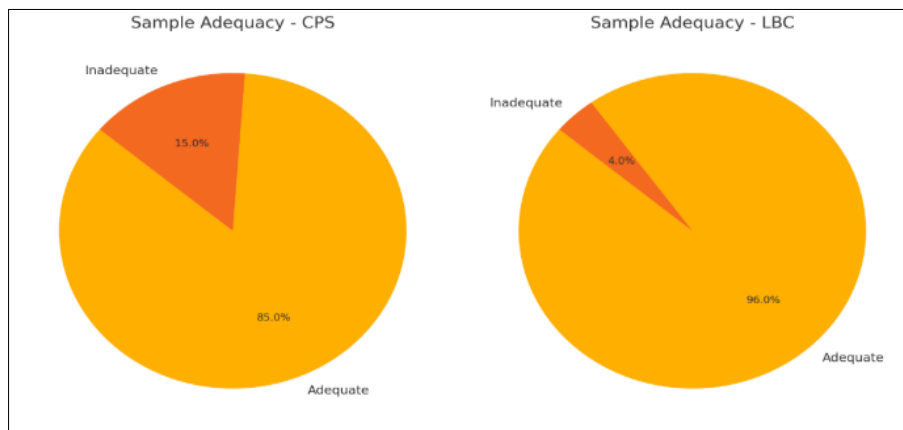


Fig 1: Comparison of Sample Adequacy between CPS and LBC methods

2. CIN Detection Rates

CIN2 detection rates differ significantly: 16% of the LBC samples showed this degree of lesion compared to 10% in the CPS samples; 8% of the LBC samples and only 5% of the CPS samples were diagnosed with CIN3. Table 2: comparing CPS and LBC for the diagnosis of CIN1, CIN2 and CIN3 with statistical analysis revealing greater LBC sensitivity than CPS for all degrees of lesion types and $P<0.05$. Also

figure 2 illustrates that HIL LBC had higher significant detection rate CIN 3 lesion.

Table 2: Comparison between CPS and LBC Detection Rates

Lesion Type	CPS (%)	LBC (%)	p-Value
CIN1	15	22	0.00
CIN2	10	16	0.02
CIN 3	5	8	0.01

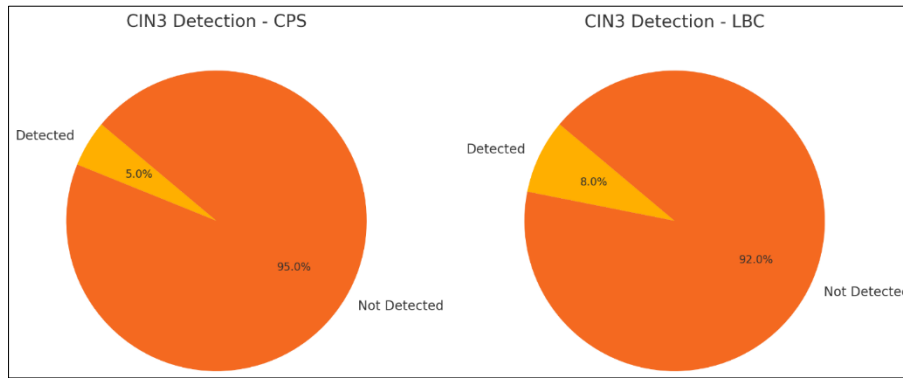


Fig 2: Comparison between CPS and LBC CIN 3 Detection Rate

3. Diagnostic Accuracy

Demonstrates high degree of sensitivity, specificity, PPV and NPV of CPS and LBC and stressing vast improvement in performance of LBC over CPS at $p < 0.05$

Table 3: Comparison of Diagnostic Accuracy between CPS and LBC

Metric	CPS (%)	LBC (%)	p-Value
Sensitivity	72	89	0.00
Specificity	68	85	0.00
Positive Predictive Value	70	88	0.01
Negative Predictive Value	75	90	0.03

4. Trends in CPS and LBC Performance across Parameters

Figure 3: present A trend analysis of CPS and LBC performances in terms of detection rates, sensitivity as well as specificity against various parameters. On this chart, it is possible to grasp the extent of performance disparities between CPS and LBC at identifying target diseases and parameters, such as detection rates for CIN1, CIN2, and CIN3; sensitivity and specificity. The trends outlined below are as follows. Figure 10: Overall Performance shows an increasing trend in LBC performance for all parameters suggesting that LBC is a better screening tool than CPS.

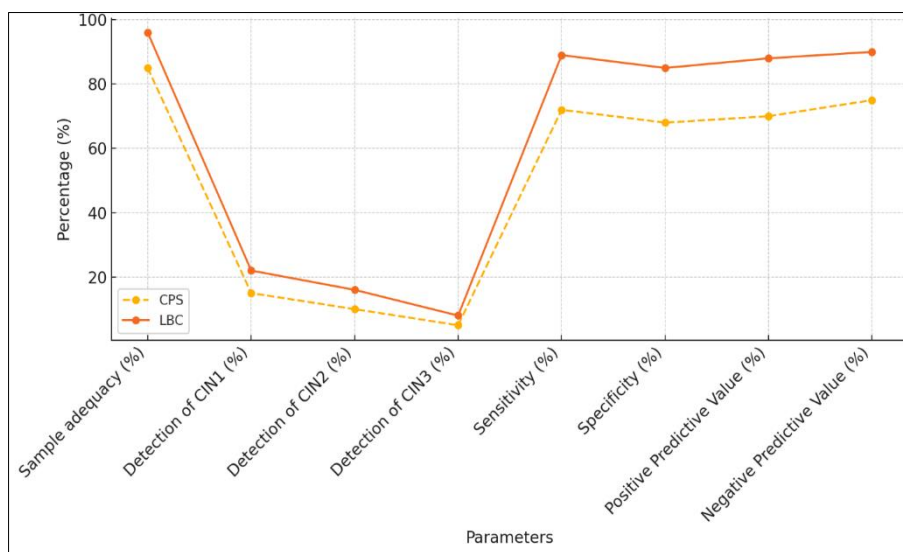


Fig 3: Trends in CPS and LBC Performance across Parameters

Discussion

Cervical cancer is one of the most preferred cancer for screening in well and medium-income countries. Its frequency and death rate of cervical cancer is down in developed nations by as much as 80% over the past five decades of community-based programs of screening for cervical cytology with Papanicolaou testing with a three to four-year interval [13]. The use of the liquid based procedure also makes it easier for instantaneous fixation and enhances visualisation of the cells [14]. The liquid-based method was proved by the Food and Drug Administration (FDA) 1996 based on split-sample analysis.

Through the performed comparison of standard endocervical scrapes with LBC for use in routine screening programs, overall cervical cancer mortality can be decreased due to

better detection and management of CIN. However, emphasis should be made on resource availability if need to be cost-efficient especially in the low development countries.

In relation to demographic characteristic of participants; Demographic data the participants were consider and assessed as to influence of attribute of the population on the research. The demographic records suggest that the young and mature age, parity, education level, and socioeconomic similarity between the CPS and the LBC groups reduces probable confounding. These results endorse the comparability of cross-sectional characteristics between both screening approaches, in line with Hassoni *et al* [12].

The current study revealed that regarding to Enhanced Sample Quality: Alcohol-based fixatives enhance not only the adequacy but also the clarity of the samples-for example,

LBC's liquid preservation rejects blood, mucus, and debris, all of which are contaminants. These clean well-preserved samples improves cytological interpretation resulting in fewer inconclusive plans and repeated testing, as seen in Arbyn *et al.*, study. Improved Incremental Yield of High-Grade Lesions: Based on the incremental yield of CIN2 and CIN3, LBC's proved to detect more severe lesions. Despite the fact that these are high-grade lesions, their early identification allows the use of ablative therapies with reduced probability of developing invasive cervical cancer similar to Saslow *et al* study [17].

Increased Sensitivity and Specificity, the sensitivity and specificity of LBC were much better as compare {as compared} to CPS. This may be attributed to the fact that LBC offers a better sample of the cellular population giving better appreciation and differentiation of the dysfunctional cells. Higher sensitivity leads to fewer false negative, which is important when the detection of high-grade lesion like CIN2 and CIN3 and which were comparable to Zhao *et al* [18] Higher Sensitivity and Specificity: LBC leads to improved accuracies to diagnose hence minimizes false negative and positive results. Improved Detection of High-Grade Lesions: Alertness when it comes to keen imaging for CIN2 and CIN3 remains a plus for LBC which will enable early treatment. Which is added with other studies identifying that the liquid-based method of sample preparation increased the cytological detection of precursors of cervical carcinoma and adequacy of the specimen compared with the traditional Papanicolaou staining technique [19]. Liquid-based method of cervical smear cytology has been found to be more sensitive than the conventional method in this study and this agreement with the finding of Ovadia and John C. Pezzullo who noted that liquid based was characterized by high sensitivity and specificity in the detection of dysplasia of the cervix than conventional method due to high sensitivity of liquid based cervical smear increased the cytological detection of atypical cervical lesions, LGSIL, HGS The conformity of the two sampling techniques with the biopsy histological study was 37 % and 53% respectively there was a significant difference between the two methods [19].

Challenges and Limitations of Liquid-Based Cytology

1. **Expectations:** LBC is costlier than CPS since it needs specific sophisticated equipment and reagents are also needed for the process. This has made its adoption in some facilities restricted due to the high costs of implementation compared to the available resources in such environment. Some guidelines have highlighted the importance of the government supporting LBC or finding an affordable solution to make it available in the areas of low-income consumers (World Health Organization [WHO] [21]).
2. **Training and Infrastructure Requirements:** LBC implementation requires training of cytologists as well as labourate technicians. Furthermore, it appears necessary to put investments in various forms of infrastructure for automated processing systems, which creates logistic concerns for health care organisations with limited financial capacity [18].
3. **Depend upon Technological Accuracy:** LBC's operations fundamentally rest upon the efficient operation of automation. It is well understood that technical hitches or maintenance problems can create sample processing problems that could impact

diagnostics results [16].

Conclusion

This work also highlights the efficacy of LBC in the diagnosis of cervical intraepithelial neoplasia in comparison with CPS. LBC has been found to be more sensitive, specific and adequate sampling than the conventional Pap smear; hence, it is the future of cervical cancer screening. The use of LBC in actually practiced cervical cancer screening can improve the specificity in particular in identifying high-grade cervical lesions.

This improvement minimizes cases of false negative that would lead to delayed management of high risk women while its superior performance is likely to yield long-term savings that result from cutting of repeat tests and invasive procedures. Decision makers in governments and healthcare organizations have to routinely assess cost Fenwick on the grounds of effectiveness to support the integration of LBC into national screening programmes. However, CPS can still be used in environments where resources especially for big hosts like Intel are scarce.

Recommendations

1. **More Making LBC Accessible:** The general way to increase utilisation of LBC strategy is by trying to find ways of cutting the cost of the programme through partnerships with companies, subsidies or coming up with cheap technologies. Further, adequate capacity for implementation of LBC should also be enhanced through training programmes of cytologists.
2. There is scope for the use of the CPS-LBC hybrid approach in the following throughput-wise in conditions of limited resources: Hybrid Screening Strategies; Given a CPS-based first-tier screening process accompanied by high-risk or marginal-results LBC testing—resource utilization may be maximized while diagnostic efficacy enhanced.
3. Future investigations should identify more efficient strategies for the implementation of LBC, cost reductions and incorporation of other tests into clinical practice; more work should be done to investigate strategies that can enhance the effectiveness of LBC, reduce its cost and add new diagnostic abilities such as HPV typing and biomarkers.

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