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Comparison of the New Synermed GluCyte™ Liquid Based Thin-Layer Preparation with both Cytyc ThinPrep™ and TriPath SurePath™ Preparations

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ABSTRACT

Introduction/ Purpose:
New, simpler and more cost effective liquid based thin-layer preparations are now available and accepted as reliable outside the USA where FDA approval is not an issue. This study evaluates and compares one such method, The GluCyte™ Method of Synermed International, Inc.(Westfield, IN and São Paulo, Brazil) to both ThinPrep™ (Cytyc Corp. Boxborough, MS) and SurePath™ (TriPath Imaging, Inc. Burlington, NC) preparations.

Materials and Methods:
The Synermed GluCyte™ Method, uses a cell dispersal, clearing and adherent solution called GluCyte™. It is a simple and reproducible manual process for slide preparation. The reagents are available for non-gynecologic cell processing in the USA. The method involves concentration by centrifugation of cells collected in Cytyc's or TriPath's preservative or in other commercially available and even "textbook" preservative fluids. Cells are re-suspended in GluCyte™ and dropped onto an unprepared clean glass microscope slide on a level surface. A uniform circle of cells dries into a thin layer of cells in a single plane which withstands the rigors of the Pap-staining process. In this study the new GluCyte™ preparations made from residual cellular material of over 300 patients were compared to the two currently "FDA approved" commercial preparation methods that have been shown to be significantly more effective than the conventional Pap smears. In a subset of the samples, cells were resuspended in an ethanol based general cytology preservative and evaluated cytologically using the GluCyte™ method and also compared using Digene's Hybrid Capture™ II HPV test.

Results and Comparisons:
The results of this evaluation were favorable, demonstrating equivalent cellular findings on paired slides from the same patient samples. The presentation of cells and infectious agents was excellent for the new preparations and diagnostic interpretations were essentially the same based upon the same standard cytologic criteria. The frequency of endocervical cells, abnormal cells and abnormal clusters on paired slides was also similar. Paired HPV tests were performed on 20 positive samples and 10 negative samples preserved in both TriPath SurePath™ preservative and a general cytology preservative. The HPV results were qualitatively the same for all 30 samples.

Conclusion:
The Synermed GluCyte™ Thin-Layer method offers a practical and less expensive alternative for thin layer, liquid-preserved cytology. Currently the Synermed product is available in the USA only for general non-gynecologic cytology preparation. In this study the GluCyte™ method of cell preparation showed similar results and compared well to both Cytyc's ThinPrep™ and TriPath's SurePath™ method in a gynecologic application. The GluCyte™ method worked well with cells preserved in Cytyc, TriPath and general cytology preservatives. HPV testing was the same for cells preserved in TriPath preservative and a general cytology preservative.

INTRODUCTION

There are currently only two liquid based cytology preparation methods that are FDA approved in the United States for gynecologic cytology and replacement of the conventional Pap smear. This factor and therefore the lack of competitive alternatives in the USA, account for much of the high relative cost of these products. Aside from the high cost of clinical trials created by the requirement of FDA approval for GYN thin-layer products, there seems to be little to justify what has clearly been a significant cost increase to routine Pap screening. These two commercial methods differ greatly in preservative and methodology but both make use of previously applied formulations and technologies that are similar to methods used in general cytology applications for many years. Liquid based cell preparation methods have traditionally been used for non-gynecologic preparations. Such are the subject of numerous textbook presentations and can be performed without overly expensive commercial reagents or apparatus. Outside of the USA similar simple manual methods are also being applied for gynecologic cytology. The two FDA approved thin-layer products are expensive and widely promoted as significantly more effective than the conventional Pap smear. This fact has been supported by numerous studies.[1] However, according to at least one recent study (Dr. John Maksem et al)[2], there continues to be significant false negative rate for the detection of SIL associated with the current ThinPrep™ market and price leader from the Cytyc Corporation. This raises the question as to whether lower cost thin-layer methods are possibly as good as or even better than the more expensive FDA approved alternatives. This study evaluates the efficacy of preparing gynecologic preparations using the Synermed GluCyte™ manual method for liquid based preparation and the diagnostic usefulness of the GluCyte™ thin layer slides. In the study of this new, less expensive method, comparison is made to both Cytyc's ThinPrep™ and TriPath's SurePath™.

METHODS

Residual material from two hundred fifty-one (251) SurePath™ preserved patient samples and fifty-two (52) ThinPrep™ preserved samples were used in the study. Known abnormal samples were selected and used to enrich the study population by combining them with randomly selected normal and unscreened cases. Low volume residual ThinPrep™ samples, suggesting low cellularity, were excluded from the study. The study was blinded to the screening cytotechnologists. In the case of both the Cytyc and TriPath residual samples, the remaining specimens were centrifuged and original preservative was decanted. The cell pellets were mixed and diluted with GluCyte™ Cell Adherent. Two drops of this mixture were then applied to a clean glass microscope slide and allowed to dry into a 16-18 mm circle. The slides were manually stained using a modified Pap stain. In all cases the cytology diagnoses were determined by cytotechnologists and cytopathologists using standard cytology criteria and compared to the original cytology results which were reported in accordance with the current Bethesda System for reporting. Discrepancies in diagnoses were carefully adjudicated by un-blinded review of paired slides by the same cytologist. In a subset of thirty patient samples (20 HPV positive samples and 10 negative HPV samples) the cells were first re-suspended in an ethanol-based general cytology preservative. These thirty samples were evaluated cytologically, but were also compared using the Digene Hybrid Capture™ II High Risk HPV Assay.

RESULTS

Three hundred three (303) residual patient samples were evaluated and compared in this study. There were 246 WNL, 27 ASCUS, 33 LSIL and 15 HSIL interpretations on one slide preparation or both. The specific comparison is presented in Table One. This presentation shows the specific correlation of individual samples grouped by Bethesda classification. There is excellent agreement of diagnoses for the paired preparations, showing agreement within one class for all samples and complete diagnostic concordance in 285 of 303 cases, or 94%. Table Two depicts a further breakdown of just those cases determined to be ASCUS by one or both preparations. This comparison shows which ASCUS cases were HPV positive or negative. The ASCUS/HPV+ ratios were about the same for the different preparation types. These tables demonstrate equivalence of performance using GluCyte™ preparations as compared to the current FDA approved preparation products. In addition to the information presented in these tables, recognition of endocervical component on the paired preparations was similar. Cytologists found the presentation of cellular material and cell morphology to be excellent on the GluCyte™ preparations. The cellularity was uniform and in a single plane with no three dimensional encumbrance to screening. Infectious agents were also easily recognized. A visual example of the macro and micro images of the GluCyte™ preparations is presented for comparison to both the Cytyc ThinPrep™ and TriPath SurePath™ preparations in Exhibits 1 and 2. Using Digene's Hybrid Capture™ II method, thirty samples (20 positive and 10 negative cases), re-suspended in the general cytology preservative, generated identical results to those obtained on the original samples.

EXHIBIT 1

GluCyte™ ThinPrep™ GluCyte™ SurePath™

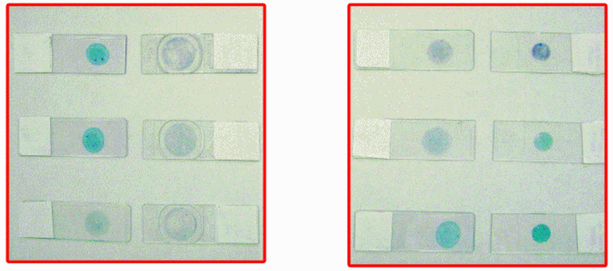


TABLE 1 FDA Approved Methodology

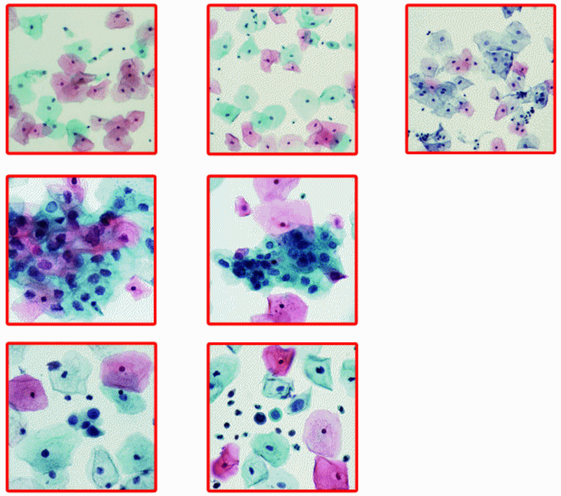
GluCyte™	WNL	ASCUS	LSIL	HSIL	Totals
WNL	233	6	0	0	239
ASCUS	7	11	1	0	19
LSIL	0	2	28	1	31
HSIL	0	0	1	13	14
Totals	240	19	30	14	303

TABLE 2 ASCUS cases with Digene Hybrid Capture II results

GluCyte™	WNL	ASCUS HPV+	ASCUS HPV-	LSIL	Totals
WNL	0	2	4	0	6
ASCUS HPV+	2	5	0	1	8
ASCUS HPV-	5	0	6	0	11
LSIL	0	2	0	0	2
Totals	7	9	10	1	27

EXHIBIT 2

GluCyte™ SurePath™ ThinPrep™



CONCLUSIONS

The Synermed GluCyte™ method is a practical alterative for non-gynecologic cytology preparations. The GluCyte™ method and products are currently not FDA approved in the USA for gynecologic use. The method, however, is practical, inexpensive and easy to use. This study supports the future value and utility of the Synermed GluCyte™ Thin-layer Liquid-based Cytology Preparation in gynecologic applications. Equivalence of sensitivity and specificity for the detection of squamous intraepithelial lesions when compared to both the Cytyc ThinPrep™ and the TriPath SurePath™ preparations, is apparent from the study results. The availability of more cost effective cytology preparation products of equivalent or better quality may play a major role in shaping the cost structure of cytology testing in the future.

REFERENCES

1. Austin, R. Marshal, Ramsy, Ibrahim: Increased Detection of Epithelial Cell Abnormalities by Liquid-Based Gynecologic Cytology Preparations- A Review of Accumulated Data. ACTA Cytol 1998;42:178-184
2. Maksem, John A., Dhanwada, Vijaya, Trueblood, Joy E., Weidmann, James, Kane, Bruce, Bolick, David R., Bedrossian, Carlos W. M. Incorporating Suspended Particles into Insoluble Thin Membranes Reveals Significant Preanalytical Error in the Automated Liquid-Based Pap Test. ACTA Cytol November 2004; Platform Presentation #17 Abstract: American Society of Cytology Meeting.