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Comparison of Diagnostic Efficacy between Cytoneph® Liquid-based Cytology and Conventional Pap Smear Cytology in Colposcopic Clinic at Chonburi Hospital

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ABSTRACT

Background: The incidence of cervical cancer is still high and continuous rising. Although conventional Pap smear has been used for Thailand's national cervical cancer screening program during the past 58 years, the incidence of cervical cancer in Thailand remains high. Evidence has shown that Liquid-base cytology can increase detection rate of precancerous lesion. However, the data is still conflicing.

Objective: This study propose to compare diagnostic efficacy of cervical cytology using conventional Pap test(CP) and Liquid-based Cytology(LBC) in the high prevalence setting. Design Diagnostic test.

Methods: 250 women with abnormal Pap smear were enrolled for cervical biopsy under colposcopy. The volunteers were randomized by computer calculation sequences. The options were put in the blinded paired numbers in seal envelope. They were performed CP and LBC then both specimens were labeled only number and were separatly sent to cytopathologist for evaluation. The correlation between cytology results and tissue diagnosis was analyzed to compare accuracy, sensitivity and specificity.

Results: The specificity was higher in LBC (37.7% vs. 56.7%) when an atypical squamous cell of undetermined significance (ASC-US) is cut-off. There was a trend toward more accuracy for LBC (70.7% vs. 76.4% p = 0.187), sensitivity was 90.4% vs. 87.5% (95%CI 83.2 -95.3% vs. 79.6 - 93.2%) for LBC and CP respectively, but no statistic significance. Unsatisfied smear found in 2 (0.8%) and 5 (2%) (p= 0.45) by CP and LBC respectively and ASC-US rate has slight decrease with LBC (10% vs. 8% p=0.53). When subgroup analyzed only test that performed first we still cannot detect superior of LBC over CP.

Conclusion: In this our high prevalence setting, the LBC has shown higher specificity. No significant difference in unsatisfactory and ASC-US rate. Larger studies and cost-effective analysis of this test in our country are necessary.

Keywords: Liquid-base cytology, Pap smear, cervical cytology, accuracy, Cytoneph

Introduction

In most developing countries, including Thailand, the incidence of cervical cancer is still high. In 2008, there were nearly 10,000 new cases[1] which claimed the second most common cancer in Thai women. Though Pap smear has been used in Thailand's national cervical cancer screening policy for the past 58 years, the incidence was not decline. Previous meta-analysis demonstrated that the sensitivity and specificity of conventional Pap smear range from 11 to 99% and 14 to 97%, respectively[2].

Liquid-based cytology (LBC) was approved by U.S. Food and Drug Administration (FDA) in 1996. Many reports have shown the superiority of LBC over conventional Pap smear (CP)[3-8]. Consequently, the National Health Service (NHS) adopted LBC as a method for cervical cancer screening. The sensitivity of LBC increased by 8-12% with fewer unsatisfied slides. Unfortunately, these results remains controversial because lack of pathological results. By contrast, subsequent studies can demonstrate neither increase sensitivity nor decline unsatisfactory results[9].

LBC is not widely available and still costly in Thailand. Cytoneph® is the LBC method that we used in this study. This second generation LBC is an only LBC method in our hospital and has been used for the past years. To our knowledge, no study has examined the accuracy, sensitivity and specificity of this test in Thailand.

To evaluate effectiveness of this newer cervical screening test at Chonburi hospital, we compared the accuracy; sensitivity and specificity between LBC and CP in colposcopic setting which tissue biopsies could be performed. Comparison of unsatisfactory rate and ASC-US rate were our secondary outcomes. We also recorded mean age and HIV infection rate as the baseline characteristics.

Materials and methods

From September 2010 to August 2011, women with history of abnormal Pap smear (ASC-US or worse) were registered and were sent to colposcopic clinic. After counselling, the participants were randomized to perform Pap smear, followed by LBC or reverse order at the same visit according to computer random number in the seal opaque enveloped. Pap smear was done by Ayre's spatula with VCE technique and fixed in 95% alcohol. Cytoneph® slide was prepared by broom-like brush that can detached and instantly drop in specific solution bottle before sent to cytologist. Both slides and bottles wererandomed sent separatly to be examined by cytologist. The results were confirmed by one of the two pathologists and were reported to interprete in the conceal envelope using Bethesda 2001 system. Inconclusive slides were discussed between pathologists. Colposcopic biopsy was done in most cases, follow the cell collection by trained colposcopist. The cytology reports were compared with highest tissue histological grading form subsequent biopsies. Cases without pathological results were excluded.

Based on 62.8%[10] accuracy of conventional Pap smear 231 cases were needed for 80% detection power of 12% increasing accuracy. Statistical analysis was calculated using SPSS v.19.0 and Medcalc v.10.2.0. Categorical data analyzed by Fisher's Exact Test and test for difference by McNemar's test.

Results

Conventional Pap and LBC slide were prepared from 290 women with abnormal Pap smear who were sent to colposcopic clinic. Forty women were excluded due to lack of histopathological results (no biopsy or hysterectomy; 32 cases were normal colposcopic findings and 8 were denied). Two hundred and fifty women were enrolled, 135 women were randomly assigned for Pap test first while 115 women were assigned in LBC first (54% vs. 46% p = 0.23). Some precolposcopic cytology reports were not performed in our hospital. They were then excluded from precolposcopic Pap results in the analysis. Women's age were ranged from 15-83 years, with mean age of 39.5 years. Comparisons of cytology results and worst histology grading are shown in Table I.

Table 1. Histology grading and cytology result.

cytology / Histology	Unsatisfied		Inflammation		ASC-US		ASC-H		LSIL		HSIL		AGC		AdenoCA		SCCA		Total
	CP	LBC	CP	LBC	CP	LBC	CP	LBC	CP	LBC	CP	LBC	CP	LBC	CP	LBC	CP	LBC	
Negative	-	2	20	27	7	5	2	-	13	7	1	2	-	1	-	-	1	-	88
CIN1	2	2	34	53	9	8	12	-	26	25	15	10	2	2	-	1	1	-	202
≥CIN2	-	1	10	13	9	7	8	7	21	17	35	39	1	3	3	7	18	11	210
Total	2	5	64	93	25	20	22	7	60	49	51	51	3	6	3	8	20	11	500

- CP: conventional Pap smear, LBC: liquid-based cytology
- AdenoCA: adenocarcinoma

All 500 slides ranging from unsatisfied smear to squamous cell carcinoma, the proportion of cytological agreement is 39.6%.Unsatisfied smear found in 2(0.8%) conventional Pap slides and 5 LBC slides (2.0%) (-1.16 to 2.55; p = 0.45) in Pap and LBC groups, respectively. We found slightly decrease ASC-US rate in LBC: 10.0% and 8.0% (95% CI -3.36 to 7.06; p = 0.53). The histologic results were groups as negative (normal, inflammation), CIN1 and ≥CIN2 (CIN2, CIN3, carcinoma in situ, microinvasive and invasive). The histological findings were negative 43 cases(17.2%), 101cases of CIN1(40.4%), 47 cases of CIN2+3 (18.8%), 45 cases of carcinoma in situ (18%) and 12 cases of microinvasive and invasive(4.8%).

Table 2. Conventional Pap smear versus Liquid-based cytology. Number (%)

		Conventional Pap smear									
		unsatisfied	Inflammation	ASC-US	ASC-H	LSIL	HSIL	AGC	AdenoCA	SCCA	Total
LBC	Unsatisfied	-	2	1	2	-	-	-	-	-	5(2%)
	Inflammation	1	41	13	9	20	6	1	-	2	93(37%)
	ASC-US	-	5	2	2	5	5	1	-	-	20(8%)
	ASC-H	-	1	1	1	1	2	-	-	1	7(2.8%)
	LSIL	1	12	4	1	22	9	-	-	-	49(19.6%)
	HSIL	-	2	3	5	10	22	-	-	9	51(20.4%)
	AGC	-	-	1	1	-	2	1	1	-	6(2.4%)
	AdenoCA	-	1	-	1	1	3	-	2	-	8(3.2%)
	SCCA	-	-	-	-	1	2	-	-	8	11(4.4%)
	Total	2(1%)	64(26%)	25(10%)	22(9%)	60(24%)	51(20%)	3(1%)	3(1%)	20(8%)	250(100%)

Overall accuracy of conventional Pap smear and LBC at ASC-US cut-off were 70.7% and 76.4% (-0.0278 to 0.142; p = 0.187), respectively. The sensitivity for≥CIN2 was 90.4% for Pap test and 87.5% for LBC. We found substantial higher specificity of LBC (56.7% (95% CI 48.1- 65.0%) than conventional Pap test. When use CIN1 as a cut-off , there was no difference in the accuracy, sensitivity or specificity. The split-sample specimen technique was shown no significant effect in these results (Table 4, 5).

Table 3. Comparison of the efficacy between conventional Pap smear and LBC for detection of high grade lesion (≥CIN2) when using different cut-off levels.

	Pap	LBC	p-value	CI
I. when use ASC-US as cut-off				
Accuracy	70.7%	76.4%	0.187	-0.0278 - 0.142
Sensitivity	90.4%	87.5%	(83.2 -95.3% vs. 79.6 - 93.2%)	
Specificity	37.7%	56.7%	(29.8 - 46.2% vs. 48.1- 65.0%)	
PPV	51.6%	59.8%	(44.1 - 59.0% vs. 51.6 - 67.7%)	
NPV	84.3%	86.0%	(73.1 - 92.2% vs. 77.3 - 92.3%)	
II.when use CIN1 as cut-off				
Accuracy	66.8%	70.1%	0.437	-0.0504 to 0.117
Sensitivity	74.2%	73.3%	(64.8 - 82.3% vs. 63.8 - 81.4%)	
Specificity	59.3%	66.9%	(50.8 - 67.3% vs. 58.6 - 74.4%)	
PPV	56.9%	61.6%	(48.2 - 65.3% vs. 52.4 - 70.1%)	
NPV	76.1%	77.6%	(67.1 - 83.6% vs. 69.2 - 84.5%)	

- PPV = Positive predictive value, NPV = Negative predictive value.
- CI: 95% Confidence Interval

Table 4. Comparison of the efficacy between conventional Pap smear and LBC for detection of high grade lesion (≥CIN2) when alternating sequence of collecting cytology.

Pap	LBC		p-value	CI
III. Pap smear perform first, ASC-US as cut-off (n=135)				
Accuracy	65.4%	73.7%	0.195,	-0.0425 to 0.208
Sensitivity	87.7%	85.7%	(75.2 - 95.3% vs. 72.7 - 94.0%)	
Specificity	43.0%	61.6%	(38.6 - 59.3% vs. 50.5 - 71.9%)	
PPV	46.7%	56.0%	(36.2 - 57.4% vs. 44.0 - 67.4%)	
NPV	86.0%	88.3%	(76.9 - 95.7% vs. 77.4 - 95.1%)	
IV. LBC perform first, ASC-US as cut-off (n=115)				
Accuracy	62.5%	70.0%	0.226,	-0.0464 to 0.196
Sensitivity	85.7%	87.5%	(72.7 - 94.0% vs. 75.9 - 94.8%)	
Specificity	61.6%	52.5%	(50.5 - 71.9% vs. 39.1 - 65.7%)	
PPV	56.0%	63.6%	(44.0 - 67.4% vs. 51.8 - 74.3%)	
NPV	88.3%	81.5%	(77.4 - 95.1% vs. 65.6 - 92.2%)	

Table 5. Comparison of the characteristics and the efficacy of conventional Pap test and Liquid-based cytology in case which either test was performed first.

	Pap	LBC	p-value
Number of cases	135	115	0.2295
Mean age (SD) years	39.63(10.85)	39.27(11.29)	0.7977
HIV infection	40(34.78%)	44(32.59%)	0.8173
Efficacy when the test is first to performed			
Unsatisfied	1(0.7%)	3 (2.6%)	0.4882
ASC-US	15(11.1%)	7 (6.1%)	0.2433
Sensitivity	87.76%	87.50%	
95% CI	75.22% to 95.34%	75.92% to 94.80%	
Specificity	43.02%	52.54%	
95% CI	32.39% to 54.15%	39.12% to 65.70%	

Discussion

To implement of cervical screening program in Thailand, test that claim more sensitivity, more specificity and cheaper should be used for prevention of cervical cancer. In 2007, there were only 8 randomized[5,8,15-20], unbiased and complete histological confirmed studies on cervical screening. Arbyn et al[9] demonstrated that LBC is neither more sensitive nor more specific than conventional Pap test. They found that some factors such as study designs (direct-to-vial, split-sample or performed both test in each woman), diagnostic cut-off levels (ASC-US or CIN2) and variety of LBC systems may effectthe interpretations[9,11]. There was a possibility that of diagnostic components are removed from the uterine cervix before the second test was performed. This study did not found better sensitivity for CIN2+. We tried to reduce any bias that may occur in a relative small study by conducting in split-sample fashion.Similar to recent report, we found no significant different in unsatisfied rate, ASC-US rate and efficacy (Table 4).

By contrast, we found significantly increase in specificity of LBC (37.7% vs 56.7%) instead of decreased one in the systematic review when use ASC-US as cut-off. This may be because of LBC system (Cytoneph®) and additional studies on this system are required to confirm this advantage.

Recent study also found no difference in diagnostic performance between conventional Pap smear and another second generation LBC[4]. That study only used histological results from single colposcopic biopsy (not include multiple biopsy or LEEP/conization or hysterectomy to analysis). Instead, our study used the worst histological results. The accuracy, sensitivity and unsatisfied percentage are concordance. Previous study showed that LBC is more convenience for cytopathologist to interpret the results by demonstrating the significant reduction of time spent for cytological diagnosis[10]. However, our study did not design to compare this difference.

The National Health Service prefers LBC technique than conventional Pap smear due to the substantial reduction in number of inadequate/ unsatisfied samples[13]. However, in our study does not show this superiority. This may be because our unsatisfied smear rate from conventional Pap smear is lower than reports from United Kingdom[6] (0.8-2.0% and 9-10%, respectively). Our sample number may be inadequate to demonstrate this advantage. We found 5 unsatisfied slides from LBC and two from conventional Pap smear. Two unsatisfied slides from LBC show "scant cells" and 3 slides had "poor stain". In contrast,

two unsatisfied conventional Pap smear slides have describes "focal drying artifact". We assume the LBC may decrease drying artifact but this test needs to improve staining quality. Another benefit from this technique is additional high risk HPV DNA detection after cytological evaluation.

In conclusion, LBC has shown higher specificity but equivalent accuracy and sensitivity at ASC-US cut-off in this our high prevalence setting. However, the number of samples is too small to detect the difference less than 12% with 80% power. Larger studies and cost-effective analysis of this test in our country are still required to improve our cervical cancer prevention programs.

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การศึกษาเปรียบเทียบประสิทธิภาพ ของการตรวจหาเซลล์ผิดปรกติด้วยของเหลว และการตรวจคัดกรองมะเร็งปากมดลูกแบบตั้งเดิม ในคลินิกห้องส่องกล้องตรวจปากมดลูก ในรพ.ชลบุรี

ภัทรวิน อรุณรัศมี, ธีระ ศิวดุลย์

วัตถุประสงค์ *: เพื่อศึกษาเปรียบเทียบประสิทธิภาพของการตรวจหาเซลล์ผิดปรกติด้วยของเหลว และการตรวจคัดกรองมะเร็งปากมดลูกแบบตั้งเดิม ในคลินิกห้องส่องกล้องตรวจปากมดลูกในโรงพยาบาลชลบุรี*

วัสดุและวิธีการ *: ในช่วงเวลาเดือนกันยายน พ.ศ.2553 –สิงหาคม พ.ศ.2554 มีผู้หญิงที่ส่งมายังห้องตรวจส่องกล้องปากมดลูกที่แผนกสูตินรีเวช โรงพยาบาลชลบุรี และได้รับการตัดชิ้นเนื้อปากมดลูกที่เข้าเกณฑ์ 250 ราย มีอายุเฉลี่ย 39.5 ปี ถูกสุ่มเพื่อเข้ารับการตรวจหาเซลล์ผิดปรกติด้วยของเหลว ก่อนหรือหลังวิธีตรวจแบบดั้งเดิม ก่อนได้รับการส่องกล้องตัดชิ้นเนื้อปากมดลูก แผ่นสไลด์และขวดบรรจุเหล่านี้ถูกปิดฉลากตัวเลขไม่ระบุชื่อ และส่งไปตรวจอ่านผลโดยนักเซลล์วิทยา และพยาธิแพทย์ ผลอ่านเซลล์เหล่านี้ จะถูกนำไปประมวลผลเปรียบเทียบกับผลชิ้นเนื้อ เพื่อคำนวณค่าความแม่นยำ ความไว และความจำเพาะต่อไป*

ผลการศึกษา *: พบว่ามีแนวโน้มที่การตรวจหาเซลล์ผิดปรกติด้วยของเหลวจะมีค่าความแม่นยำสูงกว่า การตรวจแบบดั้งเดิม เมื่อใช้ ASC-US เป็นจุดตัด (76.4% และ 70.7% p = 0.187) แต่ไม่มีนัยสำคัญทางสถิติ พบว่าค่าความไวของ การตรวจหาเซลล์ผิดปรกติด้วยของเหลว เท่ากับ 87.5% และแบบดั้งเดิม เท่ากับ 90.4% (95% CI 83.2 -95.3% vs. 79.6 - 93.2%) ซึ่งไม่ต่างกัน ส่วนความจำเพาะการตรวจหาเซลล์ผิดปรกติด้วยของเหลวและการตรวจแบบเดิมเท่ากับ 37.7% และ 56.7% ตามลำดับ การศึกษานี้ ไม่พบความต่างของการตรวจพบ ASC-US และจำนวนสไลด์ที่อ่านไม่ได้*

สรุป *: ในการศึกษาเปรียบเทียบในกลุ่มประชากรที่มีความชุกของความผิดปรกติของปากมดลูกสูง การตรวจหาเซลล์ผิดปรกติด้วยของเหลวอาจช่วยเพิ่มความจำเพาะของการตรวจพบตัวโรคมากขึ้น อย่างไรก็ตาม การศึกษานี้ยังเป็นการศึกษาที่ค่อนข้างเล็ก มีค่ากำลังในการตรวจต่ำ ยังจำเป็นต้องศึกษาเพิ่มเติมในระดับประชากรของคนไทยมากขึ้น รวมถึงการศึกษาวิเคราะห์ด้านความคุ้มค่าทางเศรษฐศาสตร์สาธารณสุขต่อไป*