

GYNAECOLOGY

Comparison between Colposcopically Directed Biopsy and Large Loop Excision of the Transformation Zone

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ABSTRACT

Objective Firstly to assess the accuracy of colposcopically directed biopsy in comparison with final diagnosis, secondly to assess correlation and agreement between colposcopically directed biopsy (CDB) and large loop excision of the transformation zone (LLETZ)

Setting Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital.

Study design Retrospective study.

Material and Method A comparative analysis was conducted from the 234 women referred to colposcopy clinic at Ramathibodi Hospital from January 1998 to December 2006, to compare between CDB and LLETZ. Accuracy was assessed by the percentage of concordance between CDB and final diagnosis. The correlation and the agreement were assessed by Spearman's rank correlation coefficient (r) and Kappa statistics (K).

Results A 89.74 % accuracy was found between CDB and final diagnosis. The correlation and the agreement between CDB and LLETZ were low ($r = 0.30$, $p < 0.0001$; $K = 0.26$, $p < 0.0001$). The CDB had overcall and undercall rates of 19.31% and 9.87%, respectively.

Conclusion Even though the correlation and agreement between CDB and LLETZ were rather low, but the accuracy was quite high. So, in our setting CDB is still of clinical use.

Keywords: LLETZ, colposcopically directed biopsy

Cervical cancer is the second most common cancer in women worldwide.⁽¹⁾ The incidence of cervical cancer has declined sharply in recent decades. At least in part, this has been due to the diagnosis and eradication of precursors or squamous intraepithelial lesion in women found to be at risk because of abnormal findings on screening cytology. Colposcopically directed biopsy (CDB) has been the standard for diagnosis of squamous intraepithelial lesion (SIL) for more than three decades, and management algorithms has been based on the

findings of these biopsies. However, since large loop excision of the transformation zone (LLETZ) for SIL was first described in 1989,⁽²⁾ the accuracy of CDB in identifying the severity of SIL has been questioned.⁽³⁻⁹⁾ LLETZ has been shown to result in the diagnosis of microinvasive cancer not identified by CDB.^(3-7,9-11) Significant underdiagnosis by CDB has been reported.⁽³⁻⁹⁾ Women with more advanced disease than that identified by CDB may receive inadequate treatment, with the risks of persistence of lesions and development of invasive cancer. The aims of

this study were to evaluate firstly the accuracy of CDB compared to final histopathological diagnosis and secondly the correlation between the histopathology of the initial directed biopsy and the histopathology in the excised transformation zone.

Materials and Methods

The patients who were examined at colposcopy clinic at Ramathibodi Hospital from January 1998 to December 2006 and underwent LLETZ treatments were reviewed. In our institute, all women with cytological abnormalities (ASCUS or worse) were counselled and underwent colposcopic examination by chief residents under the direct supervision of one gynecologic oncologist or gynecologic oncologist. The findings were documented. The punch biopsy was taken from the worst affected area via colposcopic guidance using 3% acetic acid. The indication for LLETZ as diagnostic or therapeutic procedure followed the standard protocol.⁽¹³⁾

The LLETZ was performed according to the technique described by Prendiville et al.(1989)⁽²⁾ following four quadrant infiltration of local anesthetic into the cervical tissue. The patients were excluded from the present study if they were unsuitable for local ablative treatment firstly the transformation zone was not fully visible (unsatisfactory colposcopy), secondary evidence of glandular abnormalities such as adenocarcinoma in situ (AIS), finally invasive cancer suggested from colposcopy or biopsy-confirmed invasion. Biopsy-confirmed microinvasions (MIC) from CDB were included in the present study. The final histopathological diagnosis was defined as the most severe grade of disease of all available specimens (CDB, LLETZ or hysterectomy)

Data were entered into a database and analyzed using statistical package for the social sciences (SPSS) version 11.5. Final histopathological diagnosis were used to measure the accuracy of CDB, and histological findings of LLETZ specimens were used to measure the correlation with CDB results. Kappa statistics (K) and Spearman's rank

correlation coefficient (r) were used to measure the agreement and the correlation between the grade of dysplasia from CDB and LLETZ findings. Exact agreement (K) between two procedures is reflected by a value of 0.8-1, substantial agreement; 0.6-0.79, moderate agreement; 0.4-0.59 and fair agreement; 0.2-0.39. Spearman's rank correlation coefficient (r) > 0.7 indicates high correlation, 0.4-0.7 moderate correlation and < 0.4 indicates low correlation. A p-value of less than 0.05 was considered statistically significant.

Results

During the study period, 234 patients were eligible for the present study. The mean age of patients was 38 years (SD 8.79; range 19-67 years). 51 women (21.8%) were nulliparous and 183 women (78.2%) were parous. LLETZ margins appeared to be clear in 133 women (56.84%). Margins were involved in 60 (25.64%) and not reported in 41 (17.52%) women, respectively. Margins were involved dividing to HSIL 51 (21.79%), MIC 7 (3%) and LSIL 2 (0.85%) women. Margins were involved in all MIC were received TAH and in HSIL were repeated pap smear every three month until progression or regression is established or hysterectomy remains appropriate in selected instances. The mean interval between CDB and LLETZ was 45 days.

Table 1 showed the comparison of histopathology from CDB and final diagnosis. Of the 234 women, CDB identified 8 (3.42%) with no evidence of SIL (no SIL), 22 (9.4%) with LSIL, 187 (79.91%) with high-grade SIL (HSIL) and 17 (7.27%) with MIC. The accuracy rate of CDB in comparison with final diagnosis was 89.74%. The accuracy was higher in women with HSIL and MIC (96.3% and 94.1% orderly). There were 7 cases of MIC and 1 case of invasive carcinoma that were not diagnosed by CDB. 7 patient of MIC by LLETZ were diagnosed as HSIL and 1 patient of invasive carcinoma by LLETZ was diagnosed as MIC. The percentage of women with unexpected MIC and invasion were 2.99% and 0.43%, respectively. 1 out of 234 (0.43%)

women had negative final diagnosis.

Table 2 illustrated the agreement and correlation between LLETZ and colposcopically directed biopsy in each patient, showing that the exact agreement concurred in 165 out of 233 cases (70.8%). The overcall rate at CDB was 19.31% with 9.87% undercall. The K statistics and Spearman's rank correlation coefficient for the grade of SIL on CDB and the grade of SIL on the LLETZ specimen were 0.26 and 0.30 ($p < 0.0001$), respectively. This indicated quite low agreement and correlation between the results of CDB and LLETZ findings.

Discussion

The present study illustrated the adequate accuracy of CDB in the diagnosis of SIL despite of quite low agreement and correlation with LLETZ. The rather low agreement and correlation is similar to the results of previous studies.^(3,8,9,11) Some researches showed a strong agreement and correlation.⁽¹⁰⁾ However, the better correlation in those studies did exist when the results for agreement within 1 degree were compared. In the present study, a two-tiered classification defined by The Bethesda System was used, therefore, the exact agreement was considered as the measure.

The literature reported the exact agreement of CDB comparing with excision specimen was between 35-90%.⁽³⁻¹¹⁾ The 70.8% exact agreement using LLETZ, comparing with the previous data, showed a satisfactory result and also the accuracy rate was quite high (89.74%). The agreement was poor in the no SIL and LSIL group but it was better in those with HSIL. Possible explanations for the low agreement in no SIL and LSIL group included failure of the colposcopist to take the biopsy at the most severe area, complete removal of a small low-grade lesion by CDB or abolition of lesions by inflammatory reaction following biopsy, the inability to detect a tiny subtle high-grade lesion occurring in a large striking low-grade lesion or immature metaplasia, high level of intraobserver and interobserver variability in histologic diagnosis of CIN 1.⁽⁸⁾ The possible explanations for the high

agreement in HSIL group is that lesion of HSIL tend to be larger than a low-grade lesion. Therefore, the worst affected area was easier to be identified by colposcopist. In addition, the rest of lesion is not much affected by inflammatory reaction after taking biopsy because of the size of the lesion. The influence of lesion size on the correlation was studied by Buxton et al.⁽⁴⁾

In the present study, we found that 9.87% of women with SIL on biopsy who underwent LLETZ had more severe lesions including invasion identified in LLETZ specimens. Undercall of CDB was noted in 87.5% of women with no SIL and in 40.9% of those with LSIL. This is a much worrisome finding because it could cause an under treatment. High-grade SIL was found in 21% - 42% of the excised specimen in women who were diagnosed with low-grade SIL on CDB.^(9,14-15) From the present data, 40.9%, was comparable to those reports. This indicated the disadvantage of using observational strategies to manage women with biopsy-proved low-grade SIL due to the possibility that a higher-grade lesion may be present, with an increased risk of progression. Close follow-up for those patients is mandatory and treatment with LLETZ might be more appropriate especially in clinics where compliance is poor. However we should concern that LLETZ is associated with an increased risk of overall preterm delivery, preterm delivery after premature rupture of membranes, and low birth weight infants in subsequent pregnancies at greater than 20 weeks gestation.⁽¹²⁾ So using of LLETZ would be cautious. The most serious aspect is the undiagnosed invasive cancer. In the present study, only one case (0.43%) of those with MIC on CDB had invasive carcinoma. Moreover, 7 cases of MIC were missed by CDB, but no MIC or invasive carcinoma were found in the women diagnosed as no SIL or LSIL group. All 7 cases of MIC and 1 case of invasive carcinoma underwent LLETZ, so the diagnosis of cervical carcinoma was not missed or delayed.

Several limitations bias preclude using the present results to all women undergoing colposcopy.

Women who undergo colposcopy with CDB reported as “no SIL” and “LSIL”, are usually managed by expectant policy. Only a few cases with progressive potential, suspicion of HSIL will undergo LLETZ. This selection bias might explain a high rate of HSIL diagnosed by LLETZ in those groups. In addition, a factor not considered in this analysis is the potential effect of intra- and inter-observer variability in reporting the grade of lesion. The histologic grading of SIL is well recognized that different pathologists may apply different grades to the same specimen.

To ensure consistent reporting, all specimens should be reexamined by the same pathologist. There should be concurrent pathological review as well.

In summary, even though the correlation and agreement between CDB and LLETZ were rather low, the accuracy rate was quite high. In our setting CDB is still of clinical use. Besides, in our study group all 7 undercall MIC and 1 undercall invasive cancer proceeded to LLETZ which led to adequate treatment finally.

Table 1. Histopathology of CDB and final diagnosis (N=234 cases)

CDB (n=234)	Final diagnosis					Accuracy (%)
	No SIL	LSIL	HSIL	MIC	Invasive	
No SIL (n=8)	1	2	5	0	0	12.5
LSIL (n=22)	0	13	9	0	0	59.1
HSIL (n=187)	0	0	180	7	0	96.3
MIC (n=17)	0	0	0	16	1	94.1

Table 2. Agreement and correlation of CDB histology and LLETZ histology

CDB	LLETZ				Total	Exact Agreement (%)
	No SIL	LSIL	HSIL	MIC		
No SIL	1	2	5	0	8	1 (12.5)
LSIL	0	13	9	0	22	13 (59.1)
HSIL	10	23	147	7	187	147 (78.6)
MIC	1	1	10	4	16	4 (25.0)
Total	12	39	171	11	233	165 (70.8)

The Kappa statistics = 0.26 ($p < 0.0001$)

Spearman's rank correlation coefficient = 0.30 ($p < 0.0001$)

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การศึกษาเปรียบเทียบระหว่างการตัดชิ้นเนื้อจากปากมดลูกโดยผ่านกล้องคอลโปสโคปกับการตัดปากมดลูกด้วยห่วงไฟฟ้า

วันเมษา บรรจงศิลป์, สฤกพรพรณ วิไลลักษณ์, ประทักษ์ โอประเสริฐสวัสดิ์

วัตถุประสงค์ : ประการแรกเพื่อศึกษาความแม่นยำของการตัดชิ้นเนื้อจากปากมดลูกโดยผ่านกล้องคอลโปสโคปโดยเทียบกับการวินิจฉัยขั้นสุดท้าย ประการที่สองศึกษาความสัมพันธ์ และ ความสอดคล้องระหว่างผลพยาธิวิทยาจากการตัดชิ้นเนื้อจากปากมดลูกโดยผ่านกล้องคอลโปสโคป (CDB) กับการตัดปากมดลูกด้วยห่วงไฟฟ้า (LLETZ)

ประเภทงานวิจัย : การวิจัยแบบย้อนหลัง

วัสดุและวิธีการ : เปรียบเทียบผลพยาธิวิทยาจาก CDB และ LLETZ จากผู้ป่วย 234 ราย ที่เข้ารับการรักษาน ณ โรงพยาบาลรามธิบดีระหว่างเดือนมกราคม พ.ศ.2541 ถึง เดือนธันวาคม พ.ศ.2549 การศึกษาหาความแม่นยำ ใช้การวัดร้อยละของความเหมือนกันของผลพยาธิวิทยาจาก CDB กับผลพยาธิวิทยาจากการวินิจฉัยขั้นสุดท้าย (final diagnosis) ส่วนความสัมพันธ์และความสอดคล้องวัดจากค่าสัมประสิทธิ์สหสัมพันธ์ และ Kappa statistics

ผลการวิจัย : พบว่าผลพยาธิวิทยาจาก CDB เหมือนกับ final diagnosis ร้อยละ 89.74 โดยที่มีค่าความสัมพันธ์และความสอดคล้องระหว่าง CDB และ LLETZ ค่อนข้างต่ำ โดยมีค่าสัมประสิทธิ์สหสัมพันธ์เท่ากับ 0.30 และ Kappa statistics เท่ากับ 0.26, $P < 0.0001$ ผลพยาธิวิทยาจาก CDB มีความผิดปกติ มากกว่า LLETZ ร้อยละ 19.31 และน้อยกว่า LLETZ ร้อยละ 9.87

สรุป : แม้ว่าผลพยาธิวิทยาจากการตัดชิ้นเนื้อจากปากมดลูกโดย ผ่านกล้องคอลโปสโคป(CDB) มีค่าความสัมพันธ์และความสอดคล้องกับการตัดปากมดลูกด้วยห่วงไฟฟ้า (LLETZ) ค่อนข้างต่ำ แต่ความแม่นยำจัดอยู่ในเกณฑ์ที่สูงและใช้ประโยชน์ได้