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Original Article

Pathological discrepancy between colposcopic directed cervical biopsy and Loop Electrosurgical-Excision Procedures (LEEPs) in patients with biopsies proven high grade cervical intraepithelial neoplasia

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ABSTRACT

Objective: To determine the prevalence of patients with CIN1 or less from LEEP specimens in patients with colposcopic biopsy proven CIN2 or 3.
Materials and methods: This study was a retrospective–descriptive chart review. Clinical data were retrieved from medical records of women with CIN2 or 3 from colposcopic biopsy who subsequently underwent LEEP procedure between 2004 and 2014. All pathological slides were reviewed by the gynecologic pathologist. Statistical analyses were performed.
Results: Of 210 patients, 14 patients were excluded from the study. 196 patients were in eligible criteria and data were analyzed. There were 32 patients (16.3%) with CIN1 or less from LEEP specimens who previously had colposcopic biopsies proven CIN2 or 3. Only CIN2 from biopsy was the statistically significant risk factor of CIN1 or less in LEEP specimens. Odds ratio was 10.45 (95% confidence interval: 3.28–33.33, $P < 0.001$).
Conclusion: The prevalence of patients with CIN1 or less from LEEP specimens who previously had colposcopic biopsies proven CIN2 or 3 was 16.3%. CIN2 from biopsy was the statistically significant risk factor of CIN1 or less in LEEP specimens.

Introduction

Cervical carcinoma is one of the most important problems for women's health in Thailand. It is the second most common cancer after breast cancer. The incidence of cervical carcinoma in Thailand is 24.5:100,000 (age-standardized incidence rate) and 10,000 newly detected cases, each year [1].

Many screening strategies were established with the aim to early detect preinvasive lesion before progression to invasive cancer. When abnormal pap smear is detected, colposcopy and biopsy of suspected lesion must be done to find cervical abnormality.

Patients diagnosed as high grade squamous intraepithelial lesion (HSIL) from cervical biopsy, in general, must be treated with conization. The aims of this procedure are to confirm diagnosis of cervical dysplasia and to remove all lesions if possible. Conization can be performed with electrosurgical loop (Loop Electrosurgical Excision Procedure or LEEP), a scalpel (cold knife conization) or laser (laser conization) with comparable outcomes [2].

Previous studies show that 14–26% of the patients would have CIN1 or less confirmed by LEEP in patients who had CIN2 or 3 diagnosed by cervical biopsy [3–6]. Furthermore patients who have CIN1 or less from LEEP have recurrence rate only 2–7% [6–9].

Even though conization is a safe surgical procedure, it may cause complications such as hemorrhage, infection, adjacent organs injuries. Long term complications such as cervical stenosis or incompetent cervix are also reported. Those may cause problems especially in childbearing-age women.

For the reasons mentioned above, this study objective is to evaluate the prevalence of patients with CIN1 or less in LEEP specimens from patients with colposcopic biopsies proven CIN2 or 3. We also sought to identify predictive factors of CIN1 or less from LEEPs, too.

Materials and methods

This study was a retrospective–descriptive chart review, conducted at Department of Obstetrics and Gynaecology Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The sample size was calculated using the formula to estimating single

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proportion. When the expected prevalence from the previous study was 26.9% [6]. The precision was 0.065 and $\alpha = 0.05$, the sample size plus 10% drop out was 197.

For LEEP tissue preparation, the 12 o'clock position was noted and the specimen was fixed in formalin. Entire specimen was submitted in a clockwise direction. Serially cut begins at 1 o'clock position. Total cuts were about 8–12 pieces for each LEEP specimen.

Histologic slides from colposcopic directed cervical biopsy and LEEP specimens were reviewed by one gynecologic pathologist. If there was a problem in diagnosis, another gynecologic pathologist was consulted and final diagnosis was established with agreement of both gynecologic pathologists. The results were reported according to World Health Organization criteria. Pathological discrepancy was defined as CIN2 or 3 at biopsy, but CIN1 or less from LEEP specimens.

After obtaining approval from Institutional Review Board, clinical data and pathologic slides of 210 women with CIN2 or 3 from colposcopic biopsies who subsequently underwent LEEP procedure were reviewed by the gynecologic pathologist. From the slide-review, the patients with CIN1 or less, invasive cervical cancer, adenocarcinoma in situ or adenocarcinoma from biopsies were excluded from the study. General demographic data, patient characteristics, cytology results, colposcopic findings and diagnosis including pathological results of colposcopic directed cervical biopsy and LEEP were collected. After the slide-review was completed, statistical analyses were performed.

Statistical analyses were preformed using SPSS version 14.0 (IBM SPSS Inc., Chicago, IL). The clinical data of the patients were analyzed with descriptive statistics, presented with mean ± SD, median and percent (categorical data). Chi-square test, Fisher's exact test, independent T-test, Mann–Whitney U test and Logistic regression analyses were used to analyze the relationship between CIN1 or less of LEEP-result with other clinical factors. For all analyses *P*-value<0.05 were considered statistically significant.

Results

210 patients with CIN2 or 3 from colposcopic biopsies and undergoing LEEP procedure between 2004 and 2014 were recruited. 4 patients were excluded from the study because of duplicated data. After cervical biopsies slides were reviewed, and another 10 patients were excluded (6 patients with negative or CIN1, 4 patients with invasive cervical cancer). Hence 196 patients were included in this study.

The mean age of the patient was 42 ± 13.7 years. Colposcopic diagnosis were as follows: 38 cases (19.4%) of LSIL or less, 135 cases of HSIL (68.9%) or greater, 2 cases (1%) of indecisive result and 21case (10.7%) of no data. Histologic results from biopsy shown CIN2 in 37 cases (18.9%) and CIN3 in 159 cases (81.1%). Histologic results from LEEP showed 21cases(10.7%) of no lesion, 11 cases (5.6%) of CIN1, 15 cases (7.7%) of CIN2, 131 cases (66.8%) of CIN3 and 18 cases (9.2%) with invasive cancer. Patient characteristics are listed in Table 1.

Histologic results of LEEPs showed CIN2-3 or greater in 164 cases and CIN1 or less in 32 cases. Pathological discrepancy was 16.3% between biopsy-confirmed high grade cervical intraepithelial neoplasia and LEEP result showing CIN1 or less. The margins of 32 cases with CIN1 or less from LEEPs were also reviewed and all margins were free from dysplasia.

Table 2 showed the risk factors predicting CIN1 or less in LEEP specimens. Age, HIV status, smoking, contraception methods and time interval between initial biopsy and LEEP were not related to CIN1 or less in LEEP specimens. Statistically significant differences between two groups were related to low grade cytology group ($P = 0.013$), small size of lesion from colposcopic findings ($P = 0.02$),

Table 1
Patient-characteristics (n = 196).

Characteristics	Value n (%)
Age (years)	
Mean ± SD	42 ± 13.7
Menopausal status[a]	
No	140 (71.4)
Yes	54 (27.6)
Cytological results[b]	
ASC-US	17 (8.7)
LSIL	21 (10.7)
ASC-H	36 (18.4)
HSIL	91 (46.4)
AGC	4 (2.0)
Cancer	21 (10.7)
Colposcopic diagnosis[c]	
LSIL or less	38 (19.4)
HSIL or greater	135 (68.9)
Indecisive result	2 (1.0)
Biopsy results	
CIN2	37 (18.9)
CIN3	159 (81.1)
LEEP results	
No lesion	21 (10.7)
CIN1	11 (5.6)
CIN2	15 (7.7)
CIN3	131 (66.8)
Cancer	18 (9.2)

[a] Missing data = 2.
[b] Missing data = 6.
[c] Missing data = 21.

Table 2
Risk factors predicting CIN1 or less in LEEP specimens.

	LEEP results		Total	*P*-value
	CIN1 or less	CIN2-3 or greater		
Age (years)				
(mean ± SD)	43.9 ± 14.2	45.0 ± 13.6	196	0.687[a]
HIV status				
Positive	0	10	10	0.215[b]
Negative	32	144	176	
Missing data	0	10	10	
Smoking				
Yes	3	5	8	0.128[b]
No	25	136	161	
Missing data	4	23	27	
Cytology results				
Low grade group[d]	11	27	38	0.013[b]
High grade group[e]	19	133	152	
Missing data	2	4	6	
Size of lesion from colposcopic findings				
1 quadrant or less	18	55	73	0.020[b]
2–4 quadrants	7	86	93	
Missing data	7	23	30	
Colposcopic diagnosis				
LSIL or less	13	27	40	<0.001[b]
HSIL or greater	13	122	135	
Missing data	6	15	21	
Biopsy histology				
CIN2	18	19	37	<0.001[b]
CIN3	14	145	159	
Missing data	0	0	0	
Time interval from biopsy to LEEP (days)				
(mean ± SD)	46.4 ± 28.4	53.0 ± 51.2	171	0.589[c]
Missing data	5	20	25	

[a] Student t test.
[b] Chi-square test.
[c] Mann–Whitney test.
[d] Low grade group: ASC-US, LSIL.
[e] High grade group: ASC-H, HSIL, AGC and cancer.

LSIL or less from colposcopic diagnosis ($P < 0.001$) and CIN2 from biopsy result ($P < 0.001$).

Logistic regression analyses were performed to explore the relationship mentioned above. Only biopsy histology of CIN2 was significantly related to CIN1 or less in LEEP specimens. The odds ratio was 10.45 (95% confidence interval: 3.28–33.33, $P < 0.001$). Detailed result of logistic regression analysis was shown in Table 3.

Table 3
Logistic regression analysis of Risk factor predicting CIN1 or less in LEEP specimens.

Risk factors	Odds ratios	95% Confidence interval	*P*-value
Cytology results	0.97	0.28–3.31	0.954
Size of lesion from colposcopic findings	2.66	0.91–7.79	0.074
Colposcopic diagnosis	2.25	0.77–6.58	0.140
Biopsy histology	10.45	3.28–33.33	<0.001

Discussion

CIN2 and 3 should be managed properly because these precancerous lesions have the potential to develop into cervical carcinoma. LEEP is one of many treatment modalities for preinvasive cervical disease. Failure rate of treatment and operative morbidity are comparable with other modalities [2].

Not many studies reported the absence of residual lesion or low-grade dysplasia from LEEP specimens. Our study showed 16.3% of CIN1 or less from LEEP specimens of patients with CIN2-3 proven by colposcopically guided biopsy. It is similar to previous studies [3–5] that reported 14–18% prevalence of this condition, but Zhang et al. in 2015 found higher rate (26.9%) for absence of residual lesion or low-grade dysplasia [6]. The difference in rate of CIN1 or less in our study and study of Zhang may be from different patients population.

The absence of residual dysplasia in LEEP specimens can be explained by several reason. First, the dysplastic lesion is focal and small so it is removed by punch biopsy [10]. Our study may also support this reason. In patients whose lesion located within one quadrant of cervix, the rate of CIN1 or absence of dysplasia from LEEP specimens is higher, statistically significant by univariate analysis, compared with patients whose lesion located 2 to all quadrants of cervix. The second reason is regression of the lesion. 6–50% of CIN2-3 lesions spontaneously regress [10–12] and CIN2 is more likely to spontaneously regress than CIN3 [13]. The biopsy operation itself might accelerate the regression by stimulating the immune system [6]. The third reason is the lesions are missed and not removed by LEEP, and the last reason is wrong pathological report or pathologist failed to identify area that contained CIN [5].

Our study found that cytological result, size of lesion from colposcopic findings, colposcopic diagnosis and biopsy histology were associated with CIN1 or less from LEEP specimens with statistical significance by univariate analysis. Logistic regression analyses were also performed in these variables and biopsy histology of CIN2 is the only risk factor predicting CIN1 or less in LEEP specimens. This finding is similar to study of Zhang [6] but different from study of Ryu [5]. Zhang et al. found that biopsy histology of CIN2 was the predicting factor or CIN1 or less from LEEP. However this result was not found from Ryu study. Our study evaluated CIN1 or less from LEEP while Ryu study evaluated only absence of dysplasia from LEEP. This might be the reason of the difference outcome between our and Ryu study.

Retrospective design is the limitation of this study. Several missing data were seen in the study. Other previous studies also performed laboratory investigations such as HPV viral load, HPV genotype and p16INK4a and some of these investigations were risk factors predicting CIN1 or less from LEEP specimens [5,6]. Our study did not perform any mentioned investigations. The study of p16 immunohistochemistry to determine whether this marker can be used to decrease the discordance between colposcopic cervical biopsy and LEEP results is presently being conducted [6]. Moreover colposcopic directed biopsy and LEEP were performed by different person, so the results can be interfered by competency of the physician. However our study had reasonable sample size and histological slides were reviewed by one gynecologic pathologist.

Table 4
Logistic regression analysis of risk factors predicting absence of dysplasia in LEEP specimen [9].

Risk factors	Odds ratios	95% Confidence interval		*P*-value
		Lower	Upper	
HPV HC2 viral load < 100	4.75	2.56	8.83	<0.001
HPV16	0.47	0.24	0.92	0.26

The findings could be useful for better patient counseling, especially among young women with CIN2 from cervical biopsies regarding the chance of CIN1 or less from LEEPs. However Nam et al. suggested using HPV HC2 viral load and HPV 16 as prognostic factor to predict absence of dysplasia in LEEP specimen (Table 4) [9]. This findings consistent with last ASCCP consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors that accept six-monthly observation by cytology and colposcopy for up to 12 months for young women with histologic diagnosis of CIN2-3 [14]. However, the physician has to counsel the patient carefully because of delayed treatment or observation is not standard treatment of CIN2-3 in other age groups.

In conclusion, our study showed 16.3% of CIN1 or less from LEEP specimens in patients with CIN2-3 proven by colposcopically guided biopsies CIN2 from cervical biopsy is the significant independent predictor of CIN1 or less in LEEP specimen.

Conflicts of interest

The authors have no conflict of interest.

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