

A Clinical Study of Correlation between Colposcopy Directed Punch Biopsy and Leep (Loop Electrosurgical Excision Procedure) in Cervical Intraepithelial Neoplasia

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Abstract: Cervical cancer is a preventable disease. It is also curable if detected early and adequately treated. Yet it is the fourth most common cancer among women globally. In India cervical cancer is the second most common cancer among women between 15 and 44 years of age. The most common histologic type of cervical cancer is squamous, most common cause is by HPV infection. Cervical intraepithelial neoplasia (CIN) is a premalignant condition of the uterine cervix. Various screening methods are available for diagnosis including Pap smear and colposcopic directed biopsy. However, LEEP (Loop electrosurgical excision procedure) is used for treatment of CIN. Invasive cervical cancer has a long pre invasive phase and hence early diagnosis and treatment can be done. **Objective:** This is a prospective observational study of correlation between colposcopic directed biopsy and LEEP in cervical intraepithelial neoplasia (CIN). **Methods:** A longitudinal study was conducted on 150 subjects attending Gynecological Outpatient department at tertiary care centre and who met the inclusion and exclusion criteria of reproductive age group i.e.(22-55 years) those were screened for CIN (cervical intraepithelial neoplasia) by VIA (visual inspection via acetic acid) and/or cervical cytology by liquid based cytology. All the patients with positive VIA and abnormal cervical cytology findings were subjected /screened by colposcopy examination and patients with CIN were subjected to LEEP. Kappa statistics was used to determine agreement between 2 test procedure. Spearman's correlation coefficient (ρ) was used to measure strength and direction of association between 2 test procedure based on ordered variables. P value <0.05 was considered statistically significant. **Results:** 111 patients were having cervicitis on colposcopy directed biopsy and 39 patients were diagnosed with CIN. The colposcopy directed biopsy and LEEP results were statistically significant in positive patients with CIN. No significant correlation between demographic indices and prevalence was noted in CIN patients. **Conclusion:** Colposcopic directed biopsy is the gold standard for diagnosis as confirmed by Loop electrosurgical excision procedure (LEEP), also known as large loop excision of the transformation zone (LLETZ), a method used for excisional treatment of HSIL.

Keywords: Cervical intraepithelial neoplasia, Loop electrosurgical excision procedure, Dysplasia, Colposcopy, cervical cytology

1. Introduction

Invasive cervical cancers are usually preceded by a long phase of pre invasive disease [1]. This is characterized microscopically as a spectrum of events progressing from cellular atypia to various grades of dysplasia or cervical intraepithelial neoplasia (CIN) before progression to invasive carcinoma. Cervical intraepithelial neoplasia (CIN) is a premalignant condition of the uterine cervix [2]. Down staging is defined as a process of screening for cancer using clinical approaches for early detection of this disease [3]. The Papanicolaou test (Pap smear) is a method of cervical screening used to detect potentially precancerous and cancerous lesion in the cervix. A colposcopy is a low-power, stereoscopic, binocular, field microscope with a powerful variable intensity light source that illuminates the area being examined. It is a simple noninvasive procedure. Screening is done with 5% acetic acid applied for 1 min and acetowhite areas are seen, lugol's iodine is applied over cervix and yellow areas and unstained areas are visualized. Inspection

is also done with green filter to see for abnormal vessels. These are then categorized as CIN on basis of REIDs and SWEDE score. Colposcopy is reliable in diagnosing cervical intraepithelial neoplasia in women. The reported sensitivity and specificity of colposcopy for any cervical disease was 93.9% and 51.9% respectively. The loop electrosurgical excision procedure (LEEP) is used for diagnosis and treatment of high grade cervical dysplasia (CIN II/III) discovered on colposcopy examination. The aim of this study to correlate between colposcopy directed biopsy and LEEP in cervical intraepithelial neoplasia subjects [4].

2. Methodology

It is prospective observational study performed on 150 women attending Gynecological Outpatient department at tertiary care centre who had given consent for study and met the inclusion and exclusion criteria of reproductive age group i.e.(22-55 years), those were screened for CIN (cervical intraepithelial neoplasia) by VIA (visual inspection

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via 5% acetic acid for 1 min) and/ or cervical cytology by liquid based cytology. All the patients with positive VIA and abnormal cervical cytology findings were subjected /screened by colposcopy examination. Exclusion criteria included pregnant women, women with bleeding at the time of examination, patients of cervical cancer or patients who are undergoing or have undergone treatment of cervical cancer, patients who are already treated for cervical intraepithelial lesion. Colposcopic examination of cervix was done under illumination after cleaning the vagina and cervix with cotton swabs moistened with normal saline in order to remove the discharge. Inspection of cervix was done after application of 5% acetic acid. Surface contour, margin of lesion and appearance of blood vessels were noted. Inspection with green filter to see for abnormal vessels. Cervix was painted with Lugol's iodine in a 50% dilution to differentiate between normal and abnormal areas. Colposcopic directed punch biopsy was taken from suspicious lesions or acetowhite lesion which was near the new SCJ as it was more likely to harbour the worst abnormality. After confirmation of diagnosis of CIN on colposcopy directed biopsy, these subjects underwent excisional procedures like LEEP and cervical tissue sent for histopathological examination. Kappa statistics was used to determine agreement between 2 test procedure. Spearman's correlation coefficient (rho) was used to measure strength and direction of association between 2 test procedure based on ordered variables.

3. Results

About 150 subjects were posted for colposcopy after abnormal Pap smear findings or VIA positive and followed up. Cervical cytology of these 150 subjects was done and found that 9 (6%) subjects were having a normal Pap smear report and 45 (30%) were having ASCUS and 9 (6%) had ASC-H as shown in Table no .1 . However, 40 (26.67%) subjects were diagnosed with LSIL and 47 (31.33%) were diagnosed with HSIL. Colposcopy directed biopsy was performed on these subjects. Out of these 111 subjects were diagnosed as cervicitis and hence loop excision was not performed on these subjects. Rest 39 subjects were positive (CIN1,CIN2,CIN3) on colposcopy directed biopsy which were subjected to LEEP. Histopathology on LEEP was suggestive of 2 patients of cervicitis, 13 patients of CIN1 ,17 patients were having CIN2 and 7 patients as shown in Table no 3. In Table no 4 , correlation of grade of CIN in colposcopy directed biopsy and LEEP . Out of these 39

patients, 9 out of 12 were correctly diagnosed as CIN1 with CDB, similarly 15 out of 25 patients were correctly diagnosed as CIN2 with CDB and 1 out of 2 patients were correctly diagnosed as CIN3. Table no 5 , determines correlation between REID and SWEDE score with the help of Colposcopy and directed biopsy and maximum overlapping between REID and SWEDE score was seen in CIN1,2,3 respectively.

Table 1: Distribution of study population according to PAP Smear Finding

PAP Smear	No. of Cases
Normal	9
Acus	45
ASC-H	9
Isil	40
Hsil	47

Table 3: Histopathology on LEEP. (N=39)

	No. of Cases
Cervicitis	2
CIN1	13
CIN2	17
CIN3	7

Table 2: Histopathology on colposcopy

	No. of Cases
Cervicitis	111
CIN1	21
CIN2	14
CIN3	4

Table 4: Correlation of Grade of CIN in colposcopically directed biopsies with LEEP.

Biopsy Grade	Grade at LEEP				Total
	0	1	2	3	
1	1	9	1	1	12
2	1	4	15	5	25
3	0	0	1	1	2
Total	2	13	17	7	39

Table 5: Correlation of findings of colposcopy by REID Index and Colposcopy by SWEDE score

Colposcopy findings by REID Index	Colposcopy findings by SWEDE Score			Total
	CIN1	CIN2	CIN3	
CIN1	36	4	0	40
CIN2	36	29	0	65
CIN3	10	14	21	45
Total	82	47	21	150

Table 6: Association of risk factors for predicting CIN1 or less in LEEP specimens

Risk Factors	Category	LEEP Findings				p-value
		Normal		CIN1-2-3		
		Frequency	%	Frequency	%	
Age in years	<40	1	20	4	80	0.106,NS
	≥40	1	2.94	33	97.06	
Colposcopy finding by REID Index	CIN1	0	0	5	5.41	<0.001,HS
	CIN2	2	100	2	5.41	
	CIN3	0	0	33	89.19	
Colposcopy finding by SWEDE Score	CIN1	2	100	3	8.11	0.001,HS
	CIN2	0	0	13	35.14	
	CIN3	0	0	21	56.76	
Histopathology On colposcopy	CIN1	1	50	11	29.73	0.808,NS
	CIN2	1	50	24	64.86	
	CIN3	0	0	2	7.41	

4. Discussion

Yuyeon Jung et al 667 subjects underwent cytology which resulted in HSIL, atypical squamous cells of undetermined significance (ASCUS) were 38.1% (254) and 27.1% (181) respectively, ASC-H 6.7% (45), LSIL comprising of 23.8% (159) and 4.2% of subjects were having normal pap results. Qing Cong et al diverse cytology was seen in reports of cervical cancer, out of total 670 subjects pap results were suggestive of HSIL 259 (45.4%), ASC-US 92 (16.1%), LSIL 66 (11.6%), ASC-H 53 (9.3%), squamous cell carcinoma 5 (SCC, 0.9%), AGC 5 (0.9%), AIS 2 (0.4%), and NILM 88 (negative for intraepithelial lesion or malignancy, 15.4%). In 259 cases of HSIL, 17 were HSIL (with possibility of cancer) and 2 were HSIL admixed with AGC. In our study, we found that 9 (6%) subjects were having a normal Pap smear report and 45 (30%) were having ACUS and 9 (6%) had ASC-H. However, 40 (26.67%) subjects were diagnosed with LSIL and 47 (31.33%) were diagnosed with HSIL which correlates with Yuyeon Jung et al study.^[5]

Se Ik Kim et al studied the overall concordance rate between CDB (colposcopy directed biopsy) and LEEP results was 67.7% (201/297) and under-diagnosed CDB cases were observed in 26.6% (79/297). Statistically, there was a significant difference in the diagnosis of HSIL+ in all subjects. Moreover, they demonstrated a high CDB false negative rate (12.2%; 33/270) for identifying HSIL+. L. Stewart Massad et al^[6] included 47 subjects for loop excision and compared with colposcopy directed biopsy. 28% of women had no dysplasia, only 11% had worse lesions at biopsy site. Cohen's κ statistic for biopsy grade on colposcopy and loop specimen site was 0.30 with spearman's correlation of 0.43. This indicates moderate correlation between colposcopy directed biopsy and loop excision specimen. In our study, colposcopy directed biopsy was performed on 150 subjects. Out of these 111 subjects were diagnosed as cervicitis, 39 subjects were positive on colposcopy directed biopsy were subjected to LEEP. Colposcopy was suggestive of 21 subjects (14%) with CIN1, 14 subjects (9.33%) with CIN 2 and 4 subjects (2.67%) with CIN 3. These were compared with LEEP results and found that kappa was 0.41 with agreement of 64.10% p value of 0.0001 which was highly significant and spearman's correlation was 0.53 which indicates moderate correlation between colposcopy directed biopsy and LEEP with p value of 0.0005 which was highly significant.

Zambia et al (78) using the bivariate analysis, age, education, and marital status were shown to increase the CIN risk, while in the multinomial logistic regression, unmarried status reduced risk of CIN. Our study outcomes are in contrast with the findings of a cross-sectional study that described the magnitude of CIN in Zambia which found that in the multinomial logistic regression, none of the demographic factors were associated with CIN. Sue L. Morenietal studied if all subjects went to an immediate LEEP, at most 45% of women may have had CIN 1 or less on LEEP and would have been over treated. Some studies have shown a much lower overtreatment rate when the time interval from Pap to LEEP is diminished. However, it would be difficult to advocate for immediate LEEP in study

population based on the percentages of this study. Given the propensity of HPV clearance over time, a "see-and-treat" approach deserves scrutiny. This study suggests that, when in a discrepant situation, the variable of time between the initial HSIL, Pap and LEEP may be a consideration in determining whether a LEEP is appropriate.

5. Summary

- In our study, 111 patients were having cervicitis on colposcopy directed biopsy and 39 patients were diagnosed with CIN with cervical biopsy obtained by LEEP.
- The colposcopy directed biopsy and LEEP results were statistically significant in positive patients with CIN.

6. Conclusion

Invasive cancer of cervix is considered to be preventable since it is associated with a long pre – invasive stage (CIN) making it amenable to screening and treatment. From the results of this study, it is evident that colposcopy is definitely more sensitive and accurate than Pap smear. By combining Pap smear with colposcopy, we can maximise the sensitivity and specificity of cancer cervix screening. Colposcopy in general has a role in the evaluation of women with abnormal pap smears, unhealthy cervix, and seems to be more accurate in detecting CIN. Thus colposcopy offers an excellent tool in evaluating cervical lesions. It is an easy and perspective method and its importance lies in teaching, diagnosis and management of cervical lesions, both neoplasia and non – neoplasia. There is a need to introduce and encourage the practice of colposcopy, in all medical institutions to evaluate and manage patients with clinically suspicious cervix and abnormal pap smears. In CIN2/3 detected by punch biopsy, LEEP conization allows further and more accurate histologic examination of the transformation zone. Although it goes undetected by visual inspection of the naked eye or colposcopy-directed biopsy, unsuspected invasive cancer can be detected by histopathological examination of conization masses. Colposcopic directed biopsy is the gold standard for diagnosis as confirmed by LEEP also known as LLETZ (large loop excision of transformation zone) a method used for excisional treatment of HSIL.

7. Limitations

The present study is conducted in a tertiary care centre, where the sample is selected from the population attending the Outpatient department, hence this population is not a representative of general population. Therefore when these tests are used for screening in general population the estimated sensitivity and specificity may not be achievable. CDB suggestive of cervicitis were not subjected to LEEP. The long interval between CDB and LLETZ might cause progression of the disease.

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