COLPOSCOPY- A PRIMARY ALTERNATIVE SCREENING TOOL FOR CERVICAL PRE-CANCER

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ABSTRACT

BACKGROUND

Cancer cervix is the most common and preventable malignancy in females. 80% of cases in India are detected in advanced stages. Paucity of cytologists in India is one of the important reasons for failure of screening by Pap smear. Visual Inspection of cervix with Acetic acid (VIA) and Visual Inspection of cervix with application of Lugol's Iodine (VILI) are two alternative strategies in low resource settings. Colposcopy involves the same principles of VIA and VILI under better magnification. We have hospitals with not so low resource settings, where gynaecologists are available, but cytologists are not. We need to evolve an alternative strategy appropriate to our resources such as colposcopy and guided biopsy.

The aim of the present study is to evaluate the feasibility of colposcopy as an alternative screening tool for cervical precancer. The objective of the study is therefore to compare the colposcopy with the known reference standard that is Pap smear and evaluate the sensitivity, specificity and predictive values.

MATERIALS AND METHODS

3000 women were compared with simultaneous colposcopy and Pap smear with latter as reference standard. Colposcopy-guided cervical biopsy was performed for suspicious lesions.

RESULTS

Unsatisfactory colposcopy due to nonvisualisation of transformation zone is an insignificant percentage (1.7%). The sensitivity, specificity, positive and negative predictive values of colposcopy for the threshold of normal versus all grades of abnormality (all age groups and all abnormal reports included) are 76.74%, 99.34%, 63.46% and 99.65%, respectively. Pap smear is taken as a reference standard. This is the primary objective of our study. Colposcopy-guided biopsy specimens of minor abnormal colposcopic lesions falling outside the transformation zone have not yielded any abnormal findings on histopathology. Three high-grade lesions were detected by colposcopy as well as Pap smear. They have also positively corroborated with histopathology.

CONCLUSION

Colposcopy has got a good negative predictive value. It seems to be as sensitive and specific as Pap smear for high-grade lesions. However, multicentric studies is recommended for pooled data.

KEYWORDS

Cervical Cancer Screening, Colposcopy, Guided Biopsy, Pap Smear.

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BACKGROUND

Carcinoma cervix is the commonest preventable malignancy amongst women in India. More than three-fourth of these patients are diagnosed at advanced stages leading to poor prospects of long-term survival and cure. Ever since the introduction of Pap smear by Papanicolaou and Traut in 1941,[1] this has remained the single most effective screening test. Evidence is convincing that cytological screening programmes are effective in reducing the mortality. The extent of reduction is directly proportional to the population screened.[2]

Although, Pap smear has become the accepted method of screening with significant decrease in cervical cancer incidence and death rates in the areas where mass screening was organised.[3,4] The health infrastructure and organisational aspects for such a screening programme based purely on the Pap smear are not available in India at present.[5] Analysis of population-based surveys indicate that coverage of cervical cancer screening in developing countries is on average 19% compared to 63% in developed countries and ranges from 1% in Bangladesh to 73% in Brazil. Strategies for improving cervical cancer prevention

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must be adapted to meet the specific needs of individual countries. Expanded screening maybe a viable option where sufficient infrastructure and health system access exists, but novel strategies need to be considered in other settings.[6] Large number of studies have proved the effectiveness of alternative strategies like Visual Inspection of cervix with Acetic acid (VIA) and Visual Inspection of cervix with Lugol's Iodine (VILI) in different parts of the world including India.[7]

Hans Hinselmann in 1925 introduced colposcopy as a clinical method of studying the morphological features of various cervical diseases.[8] A colposcope is a low power (magnification, usually 6-40 fold of the cervix), stereoscopic, binocular, field microscope with a powerful variable intensity light source for illumination. Colposcopy employs the same principles of visual examination, but with a better magnification than VIA and VILI. According to National Cancer Control guidelines, VIA and VILI are adopted as alternative screening strategies in low resource settings such as Primary Health Centres (PHCs) so that trained paramedical staff can be utilised for screening purpose. The present role of colposcopy in our National Cervical Cancer Screening Guidelines is for evaluation of cases with abnormal Pap smear or positive cases of VIA or VILI. These are generic guidelines and investigators can adopt them to suit the available resources and manpower.[5]

Some of our peripheral hospitals cannot be equated with low resource settings like PHCs. However, we do have hospitals where gynaecologists are authorised, but cytologists are unavailable. Colposcopy has not been evaluated as primary alternative screening tool. It has one major advantage of performing the guided biopsy or adopt see- and- treat approach in the same sitting.

Aims and Objectives

The aim of the present study is to evaluate the feasibility of colposcopy as an alternative screening tool for cervical precancer.

The objective of our study is therefore to compare the colposcopy with the known reference standard that is Pap smear and evaluate the sensitivity, specificity and predictive values.

MATERIALS AND METHODS

A total of 3000 women attending Outpatient Department of Obstetrics and Gynaecology unit of a hospital were evaluated over a period of 3 years. Married ladies between the age group 18 to 60 years were included. Pregnant women and those who had undergone hysterectomy/prior cauterisation/conisation/amputation/any other procedures on cervix and known patients of HIV infection were excluded. The study group underwent both Pap smear testing as well as colposcopy after obtaining consent. Women who had evidence of colposcopic abnormality were subjected to colposcopy-guided cervical biopsy in the same sitting. Pap smears were taken before application of acetic acid. The gynaecologist reporting colposcopy findings and the pathologist reporting the Pap smear results were mutually blinded to the findings of each other during the process of evaluation.

Colposcopy was performed in a standard manner after placing the women in lithotomy position in a comfortable hydraulic gynaecological examination couch. The cervices were inspected under colposcope with self-retaining water wet Cusco's specula of appropriate sizes. First, cervix was inspected with application of saline. Red-free filter was used to notice any atypical vasculature. Then, freshly prepared acetic acid (5%) was sprayed all over the cervix with a spraying device and inspected for any acetowhite areas or any other abnormality, which could be seen without any magnification. This was followed by inspection with colposcope serially under magnification of 5X, 10X and 20X. Lugol's iodine was applied to the cervix with cotton swab and scanned for any iodine-negative areas. First, it was ascertained whether the Transformation Zone (TZ) was seen in its entirety (360 degrees). Only when the entire TZ was seen, the colposcopic examination was taken as satisfactory. When TZ could not be seen in entirety, the examination was classified as unsatisfactory. The satisfactory colposcopic examination findings were further classified as normal colposcopy or abnormal colposcopy.

The Pap smear was performed in the standard manner using disposable Ayre's spatula and cytobrush. Both the endocervical and ectocervical smears were taken. All pap smears were examined by a single experienced cytologist. Pap smear reports were classified as normal or abnormal. Normal reports are those reports, which are negative for intraepithelial lesions or malignant cells. Abnormal reports are those, which are positive for intraepithelial lesions or malignant cells. Colposcopic findings were compared with the Pap smear reports. Pap smear report was taken as a reference standard in this study. The results are grouped under four categories- true negatives, false negatives, true positives and false positives. After obtaining these groups, sensitivity, specificity, positive and negative predictive values of colposcopy were calculated.

RESULTS

128 women had unsatisfactory colposcopy in their first visit (Table 1). Twenty seven (21%) belonged to the inflammatory group. Exact delineation of TZ was not possible due to inflammation. All responded to two weeks' course of antibiotics. In 3 women (2.3%), cervix could not be visualised properly and hence classified as unsatisfactory. Majority (98 out of 128; 76.56%) of the unsatisfactory category were due to nonvisualisation of squamocolumnar junction in the peri- and postmenopausal group. 50 responded to the course of oral oestrogens. The squamocolumnar junction migrated outside to the ectocervix. The remaining 48 participants did not respond to the oestrogens. Finally, only 51 (1.7%) women had unsatisfactory colposcopy. They were all in the peri- and postmenopausal age group. Though Pap smears were taken and endocervical curettage was performed in cases where squamocolumnar junction could not be visualised, we did not

include them in the final analysis as we had no comparative colposcopic opinion.

Out of 2949 participants, 43 had abnormal Pap smear reports (14.58 per thousand) (Table 2). Of these, the majority 27 (56.25%) were in the ASCUS (atypical squamous cells of undetermined significance) subgroup and 13 (30%) in the LSIL (low-grade squamous intraepithelial lesion) subgroup. Only 3 of them were in HSIL (high-grade squamous intraepithelial lesion) group. None of the participants in our study had ASC (H) (atypical squamous cells cannot exclude HSIL) and AGC (atypical glandular cells) or AIS (adenocarcinoma in situ) reports. All 3 HSIL belong to the age group of 40-49 years.

Out of 2949 participants, 52 participants were detected to have abnormal colposcopy (Table 3). 39 out of these were negative on histopathology and 13 were positive on histopathology of which 10 were of CIN 1 (cervical intraepithelial neoplasia) subgroup, 2 were of CIN 2 and 1 participant was detected to have microinvasive squamous cell carcinoma. The latter was re-classified as CIN 3 based on the histopathology of gross specimens of cervix after undergoing radical hysterectomy. We had three participants who were detected to have high-grade lesions and their Pap smear reports were of HSIL (Table 2 and 3).

The sensitivity, specificity, positive and negative predictive values of colposcopy for the threshold of normal versus all grades of abnormality (all age groups and all abnormal reports included) (Table 4) are 76.74%, 99.34%, 63.46% and 99.65%, respectively. Pap smear is taken as a reference standard. This is the primary objective of our study. 51 participants as shown in Table 1 with unsatisfactory colposcopy were excluded at the very beginning.

The colposcopic diagnosis is not compared with histopathology diagnosis for the purpose of calculating sensitivity, specificity and predictive values as all participants did not undergo colposcopic-guided biopsy. However, correlation between histopathology and colposcopic diagnosis is made in Table 5. 52 participants were detected to have abnormal colposcopy, some had more than one type of abnormal findings and hence total number of abnormal colposcopic findings (91) in Table 5 does not match with total number of participants with abnormal colposcopy (52) in the Table 4. Out of 91 abnormal colposcopic findings (lesions), 55 were within TZ and 36 outside TZ. 54.5% (33 out of 55) of lesions in TZ showed positive result in HPE. However, none of the lesions detected outside the TZ yielded any positive biopsy results. It is this category that has contributed to a large number of false-positive cases. Figures 1 to 3 are some of the digital images of high-grade lesions taken from the medical monitor used by us in the colposcopy OPD and Figure 4 depicts a low-grade lesion.

Age Group	Satisfactory Colposcopy (TZ* Seen 360 Degrees)			Unsatisfactory Colposcopy			
	1st Visit	2nd Visit	Total	Infl†	Scj‡ not seen	Cx§ not seen	Total
20-29 years	821	5	826	-	-	-	-
30-39 years	615	8	623	-	-	-	-
40-49 years	724	16	740	-	-	3	3
50-60 years	712	48	760		48		48
Total	**2872**	**77**	**2949**		**48**	**3**	**51**
			2949				**51**
N = 2949 + 51 = 3000 participants of the study							

Table 1. Satisfactory Versus Unsatisfactory Colposcopy

*TZ- Transformation zone.
†Infl- Inflammation of cervix.
‡Scj- Squamocolumnar junction.
§Cx- Cervix.

Age Group (in years)	NILM*	ASCUS†	ASC-H‡	LSIL§	HSIL‖	AGC**/AIS††	Total
20-29	822	4	Nil	Nil	Nil	Nil	**4**
30-39	609	9	Nil	5	Nil	Nil	**14**
40-49	722	9	Nil	6	3	Nil	**18**
50-60	753	5	Nil	2	Nil	Nil	**7**
Total	**2906**	**27**	**Nil**	**13**	**3**	**Nil**	**43**

Table 2. Summary of Pap Smear Reports

Normal
*NILM- Negative for Intraepithelial Lesions or Malignancy.

Abnormal
†ASCUS- Atypical Squamous Cells of Undetermined Significance.
‡ASC-(H)- Atypical Squamous Cells cannot exclude HSIL.
§LSIL- Low-Grade Squamous Intraepithelial Lesions.
‖HSIL- High-Grade Squamous Intraepithelial Lesions.
**AGC- Atypical Glandular Cells + atypical glandular cells favour neoplastic.
††AIS- Adenocarcinoma in Situ.

Total number of participants with abnormal colposcopy		52
Total number of negative histopathology		39
Total number of positive histopathology		13
	CIN* 1	10
	CIN 2	2
	Microinvasive	1†

Table 3. Abnormal Colposcopy Versus Histopathology

* CIN - Cervical Intraepithelial Neoplasia.

† Re-classified as CIN 3 based on the histopathology of gross specimen of cervix after undergoing radical hysterectomy at INHS Asvini.

Colposcopy	**Pap Smear Results**		**Total**
	Abnormal	**Normal**	
Abnormal	33 (TP*)	19 (FP†)	52
Normal	10 (FN‡)	2887 (TN§)	2897
Total	43	2906	2949
Sensitivity	: 76.74%		
Specificity	: 99.34%		
Positive Predictive Value (PPV)	: 63.46%		
Negative Predictive Value (NPV)	: 99.65%		

Table 4. Colposcopy Versus Pap Smear

*TP- True positive.
†FP- False positive.
‡FN- False negative.
§TN- True negative.

Colposcopic Abnormality	**Number***	**HPE†**	
A Within transformation zone		**+ve**	**-ve**
1. ACW (acetowhite)			
a Flat lesions with irregular/jagged margins	12	8-CIN 1	4
b. Micropapillary/microconvoluted	3	2-CIN 1	1
c. Dense with sharp margins (high grade)	3	2-CIN 2	-
		1-MIC‡	
2. Punctuation			
a. Fine punctuation	2	-	2
b. Coarse punctuation (high grade)	2	1-CIN 2 1-MIC	
3. Mosaic			
a. Fine mosaic	3		3
b. Coarse mosaic (high grade)	3	2-CIN 2 1-MIC	
4. Leukoplakia	0	0	0
5. Iodine negative	15	10	5
6. Atypical vessels (high grade)	2	2	-
Total	55	30	25
B. Outside Transformation Zone	Number	+ve HPE	-ve HPE
1. ACW a Flat	25	Nil	25
b Micropapillary/microconvoluted	Nil		
c. Dense (high grade)	Nil	Nil	
2. Punctuation			
a. Fine punctuation			
b. Coarse punctuation (high grade)	8		8
3. Mosaic			
a. Fine mosaic	Nil		
b. Coarse mosaic	Nil		
4. Leukoplakia	3	Nil	3
5. Iodine negative	Nil		
6. Atypical vessels	Nil		

Total	**36**	**Nil**	**36**
Grand Total A + B	**91**	**30**	**61**

Table 5. Colposcopic Abnormality and Histopathology

*Number - Number of abnormalities detected and not number of participants.
†HPE - Histopathological examination, ‡ MIC- Microinvasive carcinoma.

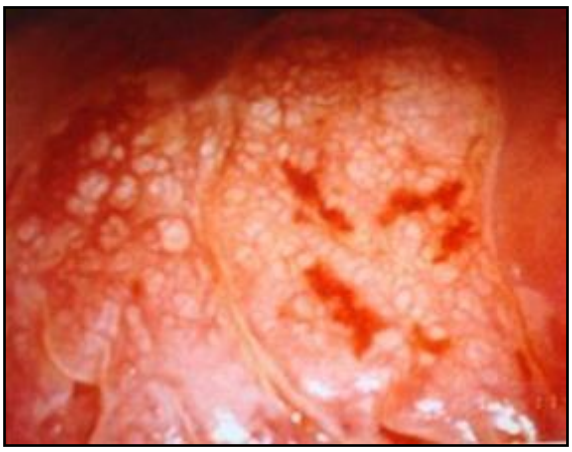

Figure 1. Photograph of High-Grade Lesion with Coarse Mosaic Pattern, Coarse Punctuations and Atypical Vessels

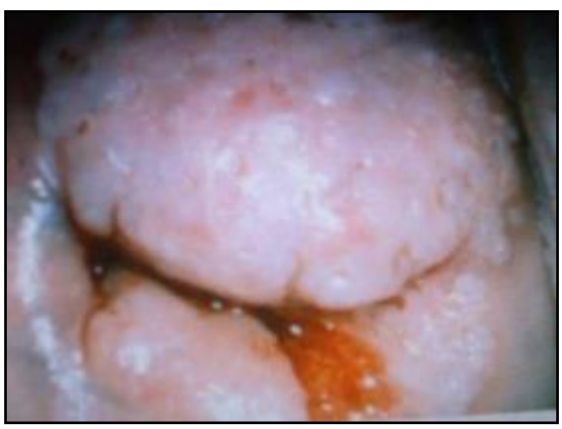

Figure 2. Photograph of High-Grade Lesion with Dense Acetowhitening

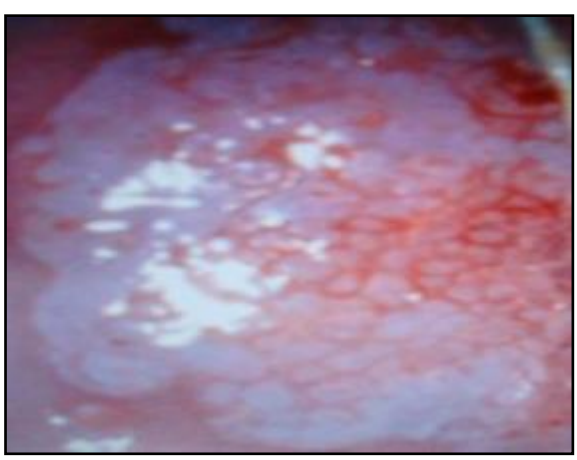

Figure 3. Photograph of a High-Grade Lesion with Dense Acetowhitening and Coarse Mosaic Pattern

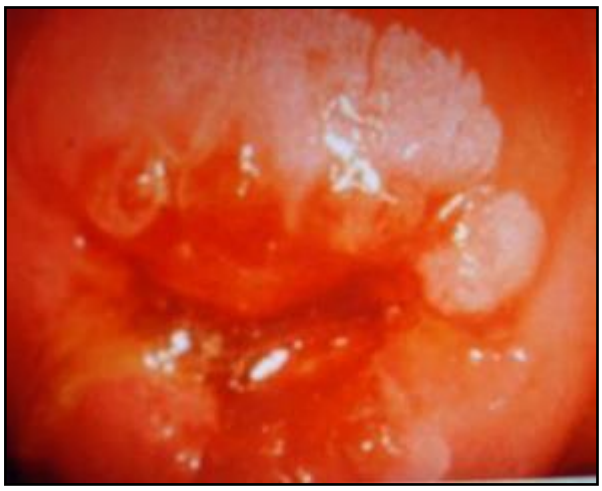

Figure 4. Photograph of a Low-Grade Lesion

DISCUSSION

Colposcopy is considered unsatisfactory if the entire transformation zone cannot be visualised or if the distal end of a lesion extending into the endocervical canal cannot be visualised. In postmenopausal women, the former is often true. In our study, the unsatisfactory colposcopy group is an insignificant percentage (1.7%) of the total study population. Oestrogen treatment will often cause enough ectropion of the endocervical cells to result in a satisfactory examination.[9] The use of endocervical speculum has been recommended by the beginner's manual on colposcopy[10] to overcome the nonvisualisation of squamocolumnar junction. We did not use endocervical speculum in our study. In our study, 14.58 per 1000 participants had reported to have abnormal pap smears, which is comparable with the ICMR, New Delhi study in which they screened women over the age of 30 years and found 5 to 15 per 1000 Pap smear abnormality.[11] The incidence of dysplasia reported at All India Institute of Medical Sciences, New Delhi, was 16 per 1000.[11] Similarly, Singh SL et al reported an incidence of 11 per 1000 women.[12]

In this study (assuming that Pap smear is 100% sensitive and specific), for all grades cervical intraepithelial lesions, the sensitivity of colposcopy is 76.74%. However, the specificity (99.34%) is comparable with Pap smear. Similarly, though the positive predictive value is less (63.46%), the negative predictive value is 99.65%, i.e. once the colposcopy is normal, the chances are 99.65% that the premalignant lesions are absent.

There is paucity of literature where research has been done to evaluate colposcopy as a primary alternative screening technique. Olayinka Babafemi Olaniyan[13] conducted a study to quantify the validity of colposcopy in the diagnosis of early cervical neoplasia by meta-analysis. Here the colposcopy is evaluated as an adjunct in cases with

abnormal Pap smear. In the meta-analysis, he analysed 8 longitudinal studies, which correlated colposcopic impression with colposcopy-guided biopsy results. The sensitivity and specificity of colposcopy for the threshold normal versus all cervical abnormalities were 87-99% and 26-87%, respectively.

An interesting observation in our study is that none of the minor colposcopic abnormalities detected outside of the transformation zone were positive on histopathology. This supports the theory that the seat of carcinogenesis is the reserve cells at the squamocolumnar junction. We have encountered 25 flat acetowhite lesions outside the transformation zone. Similarly, some fine punctuations were observed both within and outside the transformation zone. There was no acetowhitening over these areas. Subsequently, the Pap smears of these patients were suggestive of inflammatory response. Small satellite lesions (leukoplakia) outside the transformation zone were also subjected to biopsy because Pap smear reporting is not possible for the cells under these lesions and are not accessible for exfoliative cytology.

Another important observation in this study is that higher the grading of colposcopic abnormality, greater is the correlation with histopathology. We had 3 participants who were detected to have high-grade lesions and all of them correlated with histopathology as well as Pap smears reports. However, the total number of high-grade lesions are too small to draw statistical conclusions.

Olayinka Babafemi Olaniyan[13] in his meta-analysis of 8 longitudinal studies has noted that by choosing a different cut-off point where only high-grade lesions are regarded as abnormal. A fall in sensitivity is observed with a concomitant large increase in specificity. These results suggest that colposcopy is more efficient in distinguishing high-grade from low-grade lesions than in distinguishing low-grade from normal cervical tissue. For the threshold, normal and low grade SIL versus high-grade SIL, the values of sensitivity and specificity are 30-90% and 67-97%, respectively.

CONCLUSION

The present study shows that colposcopy has good negative predictive value and is sensitive and specific for detecting the high-grade lesions. Since, the primary objective is timely detection of high-grade lesions, this seems to have fulfilled in our study. However, we need pooled data to validate our study. Provision of colposcope to all hospitals where gynaecologists are available helps in a long way by reducing the morbidity and mortality of this common and preventable malignancy. It offers an advantage of adopting a 'See and Treat Approach' such as ablative procedures like cryocauterisation and large loop excision of transformation zone on cervix in the same sitting and thereby avoiding overtreatment of cases with cone biopsy or hysterectomy.

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