

Endocervicopy with Office Hysteroscope for Complete Visualization of Transformation Zone in Cases of Invisible Squamocolumnar Junction on Colposcopy

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INTRODUCTION

The incidence of CIN is gradually increasing over the years and more and more cases are being diagnosed in young women. Colposcopy is the standard of care in evaluating the cervix for premalignant and malignant lesions.^[1] Transformation zone (TZ) is the area between the original and the new squamocolumnar junction (SCJ) on the cervix.^[2] This area is of particular interest to the colposcopist due to its high rate of active immature cell proliferation resulting in increased chances of preneoplastic and neoplastic changes in this area, in fact, around 90% of cervical cancer originates here.^[2-4] Colposcopic visualization of the TZ not only helps in localizing the site of biopsy but also aids in determining the extent of the lesion and grading the severity of the lesion.

According to the new terminology for colposcopic findings given by the IFCPC (International Federation

ABSTRACT

Aim: To evaluate the role of endocervicopy for the visualization of the T3 transformation zone (TZ) on colposcopy. **Materials and Methods:** Forty patients with either abnormal Pap smear or positive VIA-VILI and T3 TZ on colposcopy were recruited from the colposcopy clinic and subjected to endocervicopy with a 4-mm office hysteroscope. The view of the endocervical canal was recorded before and after the application of 5% acetic acid and the squamocolumnar junction was identified in its entirety. An endocervical curettage was taken in all the cases and compared with the final histopathology report. **Results:** Squamocolumnar junction was visible in all the 40 cases; however, in two patients (5%), cervical dilatation had to be done. The positive predictive value (PPV) of endocervicopy in our study was 33.3% and negative predictive value (NPV) was 100%. Dense acetowhitening/irregular polypoidal endocervical mucosa with dilated blood vessels was significant in predicting the premalignant and malignant lesions with PPV of 67% and NPV of 100%. **Conclusion:** Endocervicopy allows a panoramic view of the endocervical canal. It is a safe, effective, and feasible technique for visualization of squamocolumnar junction with 5% acetic acid in cases of T3 TZ on colposcopy.

KEYWORDS: CIN, conization, endocervical curettage, endocervicopy, endocervix, squamocolumnar junction, transformation zone

for Cervical Pathology and Colposcopy) in 2011, TZ is divided into three types, i.e., T1, T2, and T3 TZ.^[5] A TZ is classified as Type 1 when it is entirely ectocervical without any endocervical portion. Type 2 TZ has an endocervical portion, but the SCJ is completely visible. In Type 3 TZ, the border between squamous and columnar epithelium is not completely visible even with the help of additional instruments.^[6]

The lesions may be missed in Type 2 and 3 TZ, which is seen in 10%–25% of women and this is a major limitation of colposcopy.^[2,3] Endocervical

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curettage (ECC) can be done to evaluate lesions within the endocervical canal, which is a blind and painful procedure with a high false-negative rate.^[7]

Various methods have been tried to visualize the entire TZ during colposcopy. These include the use of endocervical speculum, osmotic dilators including laminaria and lamicel, use of ethinyl estradiol and misoprostol. However, all these methods have a limited success rate and in around 30%–40% cases, TZ cannot be visualized completely despite using these interventions.^[8-12] Therefore, newer methods are needed that may allow the complete visualization of the morphology of the TZ and hence, a better diagnosis of CIN.

Endocervicoscopy has been proposed as a novel and promising technique for the evaluation of an incompletely visualized TZ.^[13] In this method, the conventional hysteroscope is used for evaluating the endocervical mucosa after application of 5% acetic acid using colposcopic classification system. Thus, complete extension and topography of the lesion can be assessed, thereby reducing the size of cone biopsy.

In spite of thorough literature search, no study has been found which has evaluated this technique in the Indian population and world literature is scanty. The present study thus aims to evaluate the role of Endocervicoscopy for complete visualization of TZ in cases of incompletely visualized squamocolumnar junction on colposcopy in the Indian population.

MATERIALS AND METHODS

A prospective study was conducted in the Department of Obstetrics and Gynaecology, UCMS and GTB Hospital, Delhi, from December 2013 to April 2015 as a pilot study. Ethical clearance was taken from the institutional ethical committee. This being a pilot study, the sample size was not calculated. Depending upon our colposcopy clinic data, forty women who had T3 TZ on colposcopy with either abnormal Pap smear or positive VIA-VILI were recruited from the colposcopy clinic. After taking informed and written consent, a complete medical and gynecological examination was performed.

Method of endocervicoscopy

The procedure was done under local, regional, or general anesthesia, depending on the patient profile. A 4-mm continuous-flow office hysteroscope with a 30° rod lens and 1.9 mm optic was used along with xenon light source, digital endo-camera, high-resolution monitor equipped with video recording system and with the irrigation-suction electronic device (Endomat). The cervix was exposed using a speculum, and the

mucus was wiped off with a saline-soaked cotton swab. Office hysteroscope attached to the light source and digital endo-camera was inserted into the endocervical canal. Distension of the endocervix was achieved with normal saline with a pressure set between 30 mm and 50 mm Hg. When the details were not clear, infusion pressure was increased to 80 mm and 100 mm Hg and, in some cases, even up to 150 mmHg. The view of the endocervical canal and TZ was recorded in the high-resolution monitor before the application of acetic acid. Five percentage acetic acid was then applied on the ectocervix with a cotton swab and 1 ml of 5% acetic acid was instilled through the external os using a needle-free insulin syringe. Hysteroscope was then re-introduced after waiting for a minute. A higher or lower image magnification was obtained by slowly advancing or withdrawing the instrument. The anterior and posterior-lateral walls of the endocervix were carefully examined by gently rotating the tip of the hysteroscope within the endocervix. The SCJ seen as a visible line was identified and localized in its entire path. Nabothian cysts, endocervical polyps, growth, acetowhite lesions, and suspect invasive cancer were identified. The vascularization and the morphology of the endocervical mucosa were evaluated.

Once a lesion was suspected, the tip of the optic was moved closer to get a better magnification and hence, allowing a more detailed assessment of the lesion. The hysteroscope was then removed. An ECC was taken in all the cases, and cervical biopsy from the target area was taken wherever indicated at the same sitting. According to the histopathological report, patients were then offered excisional treatment, i.e., loop electrosurgical excision procedure (LEEP), cone biopsy, hysterectomy.

Statistical analysis

1. Numerical variables have been expressed as mean \pm standard deviation
2. Predictive values of the technique were calculated by the standard formula by comparing the findings on endocervicoscopy with final histopathological diagnosis obtained on ECC or surgical specimen in cases undergoing excisional treatment (LEEP, cone biopsy, hysterectomy).

RESULTS

Forty patients who were enrolled for the study had T3 TZ with either abnormal Pap smear or positive VIA-VILI. The mean age of the patients in our study was 47.23 ± 11.32 years, with mean parity being 3.20 ± 1.60 . Nineteen patients (47.5%) were postmenopausal. Thirteen patients (32.5%) had epithelial abnormalities, of which

the most common were HSIL and LSIL (both 12.5%), followed by atypical squamous cells of undetermined significance (5%) and AGC (2.5%). On colposcopic examination, all the patients had adequate colposcopy with T3 TZ, i.e., the upper margin of TZ was inside the endocervical canal. Of the 40 patients, SCJ was partially invisible in 22 patients (55%) and completely invisible in 18 patients (45%). Colposcopic findings of the visible TZ on ectocervix were normal in two patients (5%), while the remaining 38 patients (95%) had abnormal findings, of which 30 patients had Grade 1 lesions, seven patients had Grade 2 lesions and one patient had nonspecific changes.

All the patients were subjected to endocervicoscopy with office hysteroscope (4 mm) and it was feasible in 95% of the cases as two patients (5%) required cervical dilatation who had pin-hole cervical os. Majority (70%) of the cases underwent the technique under paracervical block. In cases where additional procedure (hysteroscopy) was done, regional (17.5%) and general anesthesia (12.5%) was given. Additional hysteroscopy was performed in 14 patients (35%). There were no complications during the procedure; however, 12 (30%) patients under local anesthesia experienced mild discomfort and pain. During the procedure of endocervicoscopy, infusion pressure of 80–100 mmHg was used in most of the cases.

The SCJ was visible in 95% of cases after endocervicoscopy, which was the primary objective of our study. Two (5%) patients required cervical dilatation due to pin-hole os. Panoramic view of the endocervical canal was visualized in every case and invariably canal looked like a tunnel [Figure 1]. However, it was not possible to delineate the entire SCJ (360°) at one particular time. At a time, only a quarter of SCJ could be made visible. To have the 360° view of the SCJ, hysteroscope and the light cable had to be rotated.

The findings on endocervicoscopy were normal in 12 patients (30%), ten patients had polyp (25%), 15 patients (37.5%) had acetowhite lesions on the application of 5% acetic acid, while three patients had findings suggestive of suspect invasive cancer, i.e., irregular polypoidal mucosa with dilated blood vessels and dense acetowhitening [Figures 2, 3 and Table 1]. Abnormal endocervicoscopy is defined as the presence of acetowhite lesions with/without dilated blood vessels or suspect invasive cancer. Polyps without acetowhitening were not considered abnormal.

All the patients were then subjected to ECC and the results from the histopathology reports of ECC were compared with the endocervicoscopy findings [Table 2]. In eight patients, 2 with normal findings and six



Figure 1: Tunnel like appearance of normal endocervical canal

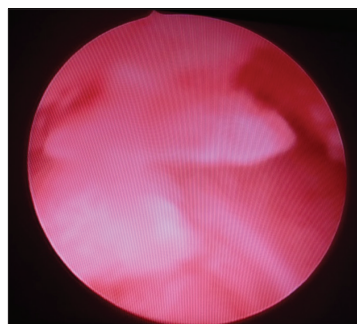


Figure 2: Endocervical polyp

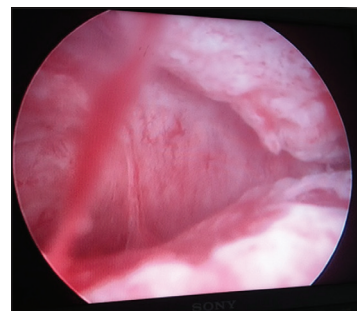


Figure 3: Suspect invasive cancer (irregular polypoidal mucosa with dilated blood vessels and dense acetowhitening)

patients with thin acetowhitening, scanty curettings were obtained; hence, histopathological opinion was not possible in these cases and was excluded from the analysis.

Out of four positive cases on histopathology, three patients had adenocarcinoma and one patient had CIN-III. None of the patients with adenocarcinoma had invasive features on Pap smear or colposcopy. However, endocervicoscopy enabled us to diagnose these positive cases. Two patients showed suspect invasive cancer on endocervicoscopy and one patient had dense acetowhitening with dilated blood vessels. Patient with CIN III had dense acetowhitening without dilated blood vessels.

The diagnosis was further confirmed on hysterectomy/ LEEP specimens [Table 3].

The positive predictive value (PPV) of endocervicopy in our study was 33.3% and negative predictive value (NPV) was 100%. Thin acetowhitening did not reveal any malignant or its precursor lesions on histopathology, thereby indicating that it is an insignificant finding. Dense acetowhitening/irregular polypoidal endocervical mucosa with dilated blood vessels was significant in predicting the premalignant and malignant lesions with PPV of 67% and NPV of 100% [Table 4].

DISCUSSION

Colposcopy is the mainstay for diagnosis and

complementary to Pap smear cytology and VIA-VILI for the diagnosis of cervical cancer precursors.^[14]

HPV testing for primary screening has not been universally implemented in India because of its high cost. However, utility of colposcopy is limited in a significant (10%–25%) number of cases where SCJ recedes into the endocervix.^[2,3] The assessment of the endocervical canal has constantly posed several diagnostic and analytic issues. Blind techniques (liquid-based phase cytology/ECC) and direct visualization-based techniques (microcolpohysteroscopy) have been widely used, showing significant diagnostic limitations.^[15]

The ECC has been conventionally used method to study the endocervix but being a blind procedure, and it has high false-negative findings due to difficult and incomplete sampling of endocervical mucosa. In around 12% of cases, the sampling leads to incomplete tissue retrieval.^[7] The procedure is painful and is usually performed under local or GA.

Microcolpohysteroscopy is another method based on direct visualization of *in vivo* cell morphology of the endocervix and SCJ. However, the technique shows low sensitivity and requires advanced skills in cytopathology and hence, rarely used.^[15]

Hysteroscopy has been widely used for evaluation of the uterus and endocervix; however, the use of office hysteroscope to visualize squamocolumnar junction in

Table 1: Findings on endocervicopy

Findings	n=40, n (%)
Normal	12 (30.0)
Polypoidal	10 (25.0)
Polyps with DBV in endocervix	2 (5.0)
Polypoidal without DBV in endocervix	8 (20.0)
Acetowhite lesions	15 (37.5)
Thin	12 (30.0)
With DBV	3 (7.5)
Without DBV	9 (22.5)
Dense	3 (7.5)
With DBV	2 (5.0)
Without DBV	1 (2.5)
Suspect invasive cancer (irregular polypoidal mucosa with DBV and dense acetowhitening)	3 (7.5)

DBV: Dilated blood vessels

Table 2: Histopathology on endocervical curettage in women with positive findings on endocervicopy

Findings on endocervico-scopy	Number of patients (n=28), n (%)	HPE report on ECC					Adeno-carcinoma
		Scanty (inadequate for opinion)	Benign	CIN			
				I	II	III	
Polyps with or without DBV	10 (35.7)	0	10	0	0	0	0
Acetowhitening	15 (53.5)						
Thin with or without DBV	12 (42.8)	6	6	0	0	0	0
Dense with or without DBV	3 (10.7)	0	1	0	0	1	1
Suspect invasive cancer	3 (10.7)	0	1	0	0	0	2

ECC: Endocervical curettage

Table 3: Work up of premalignant and malignant cases on HPE (n=4)

Pap smear	Colposcopic findings	Findings on endocervicopy	Diagnosis on ECC and cervical biopsy	Treatment given	Final diagnosis
HSIL	T3 TZ Grade II acetowhite lesions	Suspect invasive cancer	Adenocarcinoma	Radical hysterectomy	Adenocarcinoma
AGC	T3 TZ Grade II acetowhite lesions	Suspect invasive cancer	Adenocarcinoma	Radical hysterectomy	Adenocarcinoma
HSIL	T3 TZ Grade II acetowhite lesions	Dense acetowhitening with dilated blood vessels	Adenocarcinoma	Radical hysterectomy	Adenocarcinoma
HSIL	T3 TZ Grade II acetowhite lesions	Dense acetowhitening without DBV	CIN-III	LEEP	CIN III

ECC: Endocervical curettage

Table 4: Predictive values of abnormal endocervicoscopy*

Findings on endocervicoscopy	n=32, n (%)#	Premalignant and malignant lesion on HPE	Benign lesion on HPE
Normal	20 (62.5)	0	20
Abnormal	12 (37.5)	4	8

*Abnormal endocervicoscopy is defined when there was acetowhite lesion with or without DBV or suspect invasive cancer. Polyps without acetowhitenings were not considered abnormal, #Eight patients had scanty curettings and were excluded from the analysis

cases of T3 TZ is a new concept. The present study was conducted to evaluate the role of a new technique of endocervicoscopy using office hysteroscope for complete visualization of TZ in cases of the invisible squamocolumnar junction on colposcopy.

The idea of using office hysteroscope and 5% acetic acid to visualize the SCJ in T3 TZ was introduced by Bifulco *et al.* in 2010.^[13] They used this technique in young women with high-grade squamous intraepithelial lesions and took targeted biopsies. They were able to precisely locate the lesion and tailor the length of the cone, thereby preserving the future fertility in these women. However, no mention has been made in their study about the percentage of complete visibility of SCJ. Sharma *et al.* in 1995 used microcolpohysteroscopy in 45 patients with dysplasia. The technique was able to evaluate the endocervical SCJ in all cases of unsatisfactory colposcopy rendering the success rate to be 100%.^[15] Valli *et al.* in 2013 used cervicoscopy and microcolposcopy with Waterman blue dye in 119 patients of LSIL with negative or unsatisfactory colposcopy. They reported the visualization of SCJ in 115 (96.6%) patients. In four patients (3.4%), the SCJ visualization was not possible because of stenosis of cervical os due to previous cervical surgery.^[16] In our study, there was no patient with previous cervical surgery, and we achieved complete visualization of SCJ in 100 (95%) of cases.

Endocervicoscopy has the advantage of visualizing the morphology of the whole endocervical canal. The panoramic view of the canal allows the inspection of the canal in its entire path. The normal canal has a tunnel-like appearance with the presence of longitudinal crests of the endocervical mucosa known as plicae palmatae and secondary oblique branching of the mucosa constituting arbor vitae.

In our study, 12 patients (30%) had normal findings with no suspected lesion and endocervical polyps were identified in 10 (25%) cases. Acetowhitenings was observed in 15 (37.5%) patients and suspect invasive

cancer in 3 (7.5%) patients. However, we did not find jump lesions in any case. Bifulco *et al.* reported three jump lesions in their study.^[13] This could be because majority of their study population was HSIL on cytology and the number of cases was also double than ours.

ECC was done in all the cases and cervical biopsy was taken wherever indicated at the same sitting. In our study, 20% of patients had scanty curettings and were inadequate for opinion. Most of the cases with scanty curettings had normal endocervicoscopy or mild acetowhitenings of the endocervical mucosa.

All the patients with normal findings on endocervicoscopy and adequate curettings had benign lesions on histopathology. None of the patients with polyps or mild acetowhitenings revealed any premalignant or malignant lesion on histology. All patients with premalignant or malignant lesions on final histopathology (adenocarcinoma in three patients and CIN III in one patient) showed dense acetowhitenings and irregular polypoidal mucosa on endocervicoscopy. The presence of dilated blood vessels was not predictive of malignancy and was significant only when associated with dense acetowhitenings or irregular polypoidal endocervical mucosa.

The PPV of endocervicoscopy in our study was 33.3% and NPV was 100%. This was in contrast to the study done by Bifulco *et al.* who reported the PPV to be 99% and NPV to be 51%.^[13] This difference could be because in our study, the final histopathological diagnosis was based on the results of endocervical curettings, which has high false-negative rates, whereas, Bifulco *et al.* used the cone biopsy specimen for the final histology report, which is more sensitive in predicting premalignant or malignant lesions. We did not calculate the NPV as ECC has high false negatives, We observed that abnormal findings in the form of dense acetowhitenings/irregular polypoidal endocervical mucosa with dilated blood vessels were significant in predicting the premalignant and malignant lesions with PPV of 67% and NPV of 100%. It is noteworthy that none of the cases of adenocarcinoma had invasive features on Pap smear and colposcopy and they were diagnosed by abnormal findings on endocervicoscopy. Mild thin acetowhitenings was not associated with premalignant/malignant lesions on histopathology, thereby indicating that it is not a significant finding.

The strength of our study is that it is an innovative method of endocervicoscopy with 5% acetic acid application introduced by Bifulco *et al.* has been used where a novel idea of staining endocervical canal with 5% acetic acid and visualizing the SCJ with office

hysteroscope in cases of T3 TZ is used to visualize SCJ in T3 TZ.

After we completed our study, a prospective study by other authors has been published highlighting the utility of endocervicopy in evaluation of cases of abnormal cytology/HPV positivity for high-risk strains with T3 TZ on colposcopy and concluded that it is a reliable method to detect the TZ in patients with type 3 TZ and unsatisfactory colposcopy.^[17] The strength of our study is that we have used innovative method of endocervicopy using 5% acetic acid introduced by Bifulco *et al.*

The weakness of this study lies in the fact that the final histopathological diagnosis was based on the histopathology of endocervical curettings, which has high false-negative rate. This single-center study had small sample size.

CONCLUSION

Our study shows that endocervicopy with office hysteroscope appears to be safe, effective, and feasible technique for visualization of complete SCJ in women with T3 TZ. It has the advantage of delineating the complete morphology of the endocervical canal and precisely localizing any abnormal lesions which might get missed on colposcopy in women with T3 TZ. However, more studies need to be conducted with a larger sample size.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Singer A, Monaghan JM, Quek SC, Deery AR. Lower Genital Precancer: Colposcopy, Pathology and Treatment. 2nd ed. Blackwell Science, 2000.
2. O'Connor DM. Normal transformation zone. In: Apgar BS, Brotzman GL, Spitzer M, editors. Colposcopy, Principles and Practice: An Integrated Textbook and Atlas. 2nd ed. Philadelphia, PA: Saunders Elsevier Press; 2008. p. 133.
3. Rocelson B, Krumholz BA. The unsatisfactory colposcopy examination. J Reprod Med 1983;28:131-3.
4. Bappa LA, Yakasai IA. Colposcopy: The scientific basis. Ann Afr Med 2013;12:86-9.
5. Bornstein J, Bentley J, Bösze P, Girardi F, Haefner H, Menton M, *et al.* 2011 colposcopic terminology of the international federation for cervical pathology and colposcopy. Obstet Gynecol 2012;120:166-72.
6. Quaas J, Reich O, Küppers V. Explanation and use of the Rio 2011 colposcopy nomenclature of the IFCPC (International Federation for Cervical Pathology and Colposcopy): Comments on the general colposcopic assessment of the uterine cervix: Adequate/inadequate; squamocolumnar junction; transformation zone. Geburtshilfe Frauenheilkd 2014;74:1090-2.
7. Lastra RR, Meykler SE, Baloch ZW, Barroeta JE. Increasing the sensitivity of endocervical curettings by performing ThinPrep® Pap on transport container fluid: Is diagnostic material going down the drain? Cytopathology 2015;26:368-72.
8. Borgatta L, Lopatinsky I, Shaw FM. Overcoming unsatisfactory colposcopy. Use of osmotic dilators. J Reprod Med 1997;42:271-5.
9. Johnson N, Crompton AC. A new way to expose endocervical lesions at colposcopy. Gynecol Oncol 1990;36:217-8.
10. Prendiville WJ, Davies WA, Davies JO, Shepherd AM. Medical dilatation of the non-pregnant cervix: The effect of ethinyl oestradiol on the visibility of the transformation zone. Br J Obstet Gynaecol 1986;93:508-11.
11. Aggarwal R, Suneja A, Agarwal N, Mishra K. Role of misoprostol in overcoming an unsatisfactory colposcopy: A randomized double-blind placebo-controlled clinical trial. Gynecol Obstet Invest 2006;62:115-20.
12. Thanappapras D, Wilailak S, Ayudhya NI, Lertkachonsuk AA, Likittanasombut P, Chittithaworn S, *et al.* Can vaginal misoprostol effectively increase rate of a satisfactory colposcopy? A randomized double-blind placebo-controlled trial. Jpn J Clin Oncol 2010;40:203-7.
13. Bifulco G, Piccoli R, Lavitola G, Di Spiezio Sardo A, Spinelli M, Cavallaro A, *et al.* Endocervicopy: A new technique for the diagnostic work-up of cervical intraepithelial neoplasia allowing a tailored excisional therapy in young fertile women. Fertil Steril 2010;94:2726-31.
14. Greenberg MD. Reid's colposcopic index. In: Apgar BS, Brotzman GL, Spitzer M, editors. Colposcopy: Principles and Practice: An Integrated Textbook and Atlas. 1st ed. Philadelphia, PA: WB Saunders; 2002. p. 213-24.
15. Sharma R, Mittal S, Kriplani A, Buckshee K. Microcolposcopy compared with colposcopy in evaluation of abnormal cervical cytology. Indian J Cancer 1995;32:131-4.
16. Valli E, Fabbri G, Centonze C, Bompiani A, Baiocco F, Larciprete G, *et al.* Cervicopy and microcolposcopy in the evaluation of squamo columnar junction and cervical canal in LSIL patients with inadequate or negative colposcopy. Int J Biomed Sci 2013;9:148-52.
17. Rahimi S, Marani C, Gardner F, Yeoh CC, Akaev I, Votano S. Endocervicopy and biopsy to detect cervical intraepithelial squamous neoplasia in nonvisible squamocolumnar junction with unsatisfactory colposcopy: A pilot study. Technol Cancer Res Treat 2018;17:1533034617753811.