

Comparison of Vaginal versus Oral Estradiol Administration in Improving the Visualization of Transformation Zone (TZ) during Colposcopy

SEEMA BENIWAL¹, BINNI MAKKAR², SWARAJ BATRA³, GAURI GANDHI⁴, DEEPTI GOSWAMI⁵, VIJAY ZUTSHI⁶

ABSTRACT

Introduction: Colposcopy is an important diagnostic tool in the evaluation of patients with abnormal pap smears. However, in 10-20% transformation zone (TZ)/squamo-columnar junction is not completely visualized and these patients are deemed to have an incomplete colposcopy examination. Such patients usually require conization, a procedure associated with significant morbidity. Various agents like misoprostol, estrogens and laminaria tents have been used in the past to overcome the non-visualization of TZ.

Aim: The present study was conducted with the aim to compare the efficacy of vaginal versus oral estradiol administration in overcoming incomplete colposcopy.

Materials and Methods: Forty patients with non/partially visualized TZ during colposcopy were recruited for the study. These

patients were randomly distributed into two groups: In Group I, 25µg estradiol was administered intravaginally daily for seven consecutive days followed by a repeat colposcopy on day 8. In Group II, a seven day course of 25µg oral estradiol was followed by a repeat colposcopy on day 8. The efficacy of the two regimens in improving visualization of the TZ on colposcopy and their adverse effect profile was compared.

Results: Vaginal estradiol had an overall efficacy of 70% in improving visualization of the TZ as compared to oral estradiol which was effective in 50% of patients (p-value-0.19). Major adverse effects in both the group of patients were nausea and vaginal discharge with no significant differences among the two groups.

Conclusion: Both vaginal and oral estrogens had comparable efficacy and similar adverse effect profile in improving visualization of the TZ.

Keywords: Cervical cancer, Estrogens, Squamo-columnar junction

INTRODUCTION

Cervical cancer is a major cause of mortality from cancer among women, especially in the developing world. Prevalence of cervical cancer has decreased significantly with the use of screening methods like the Pap test [1]. Colposcopy is an important diagnostic tool in the evaluation of patients with abnormal Pap smears. During a colposcopy procedure, it is crucial to visualize the entire transformation zone (TZ) as almost all manifestations of cervical carcinogenesis occur there. In roughly 10-20% of all patients, the entire transformation zone is not completely visualized [2-4], rendering the colposcopic examination incomplete and inconclusive. In such patients, cone biopsy is warranted for further diagnosis and management. Conization procedure carries significant morbidity, with potential complications like bleeding, infection and incompetent cervix. In order to minimize the use of conization and its associated complications, various techniques are used to improve the visualization of transformation zone like the use of endocervical speculums, osmotic dilatation and agents such as misoprostol and estradiol. In the present study, comparison of vaginal versus oral estradiol was done in overcoming non-visualization of the transformation zone.

MATERIALS AND METHODS

The present study was a prospective randomized controlled trial conducted at a tertiary care hospital in New Delhi, India between 2009 and 2011. The study was conducted according to the principles of the Declaration of Helsinki and was approved by institutional ethical committee. Informed consent was taken from all the subjects. Sample size calculation was performed as per following hypothesis: based on a previous study by Aggarwal et al., assuming the difference in the efficacy of misoprostol compared

to placebo in improving the visualization of the TZ to be 48.9% (78.9% with misoprostol and 30% with placebo), an alpha error of 0.05% and power of 80%, the study would require a minimum of 40 subjects who would be randomized into two groups [5].

Based on the initial clinical evaluation, 250 patients were screened with colposcopy. Indications for colposcopic examination included: unhealthy/ suspicious looking cervix on speculum examination, persistent discharge per vaginum not responding to conservative therapy, postcoital bleeding and postmenopausal females with inflammatory Pap smear. Pap smear examination was performed in all the study subjects. Of these, 40 patients who were found to have partial/non-visualization of transformation zone on colposcopic examination were serially recruited for the study. Recruitment was stopped once the minimum sample size criterion was met. Further, these subjects were allocated into two groups by a computerized randomization. In Group I, 25 µg Estradiol (E2, Sun Pharma) tablets were administered intravaginally by the patients for seven consecutive days and a repeat colposcopy was done on day 8. In group II, patients were prescribed 25µg of oral Estradiol (Lynoral, Sun Pharma) daily for seven consecutive days and a repeat colposcopy was done on day 8. The efficacy of the 2 regimens in improving the visualization of TZ and their adverse effect profile were compared. In addition, following prespecified subgroup analysis was done for the following: lips of the cervix (anterior or posterior) responding or not responding to the regimen. All abnormal areas (with Reid's score ≥ 3) visualized on the cervix were biopsied and sent for histopathological examination. All patients who had persistent incomplete colposcopy despite the study drug administration underwent a colposcopy directed biopsy with endocervical curettage.

Following patients were excluded from the study: pregnant women, females with history of breast cancer, women with obvious growth on the cervix, females with coagulation disorders and hypertensive patients.

RESULTS

Out of the total 250 patients screened with colposcopy, 40 had incomplete colposcopy exam due to either partial or non-visualization of the entire TZ, giving an overall incidence of incomplete colposcopy to be 16% [Table/Fig-1]. Mean age in Groups I and II was 44 ± 3.4 years and 46 ± 2.6 years respectively (p-value 0.2). Both the groups were comparable in age distribution, parity and menstrual status [Table/Fig-2]. The efficacy of vaginal estradiol regimen was 70% as compared to 50% with the oral estradiol in overcoming incomplete colposcopy. However the difference was not statistically significant [Table/Fig-2]. Major adverse effects in the two groups included nausea and discharge per vaginum and their incidence was comparable [Table/Fig-2]. The response to the drug in relation to site of incomplete colposcopy has been described in [Table/Fig-3] and the final outcome for all patients is depicted in [Table/Fig-4].

DISCUSSION

Colposcopy has been an important method for evaluation of patients with abnormal Pap smear. According to the latest IFCPC [6] (International Federation Cervical Pathology and Colposcopy) guidelines, colposcopy examination should be assessed for 3 variables: adequate or inadequate with the reason cited (e.g., cervix obscured by blood/scarring), visibility of squamo-columnar junction and the transformation zone type. If the transformation zone/squamo-columnar junction is not completely visualized, it becomes necessary to perform conization. Such procedures are associated with significant morbidity and also, an adverse effect on reproductive potential. There have been few trials [7-10], which explored the utility of estrogens in improving visualization of the transformation zone during colposcopy. In a study by Saunders et al., 34 patients with partial or non-visualized transformation zone were administered either 30 µg of estradiol or placebo tablets daily for 10 consecutive days [7]. The overall response

Menstrual status	Unsatisfactory colposcopy (n=40)	Satisfactory colposcopy (n=210)	Total (n=250)
Premenopausal	15(7.3%)	189(92.7%)	204
Postmenopausal	25(54%)	21(46%)	46

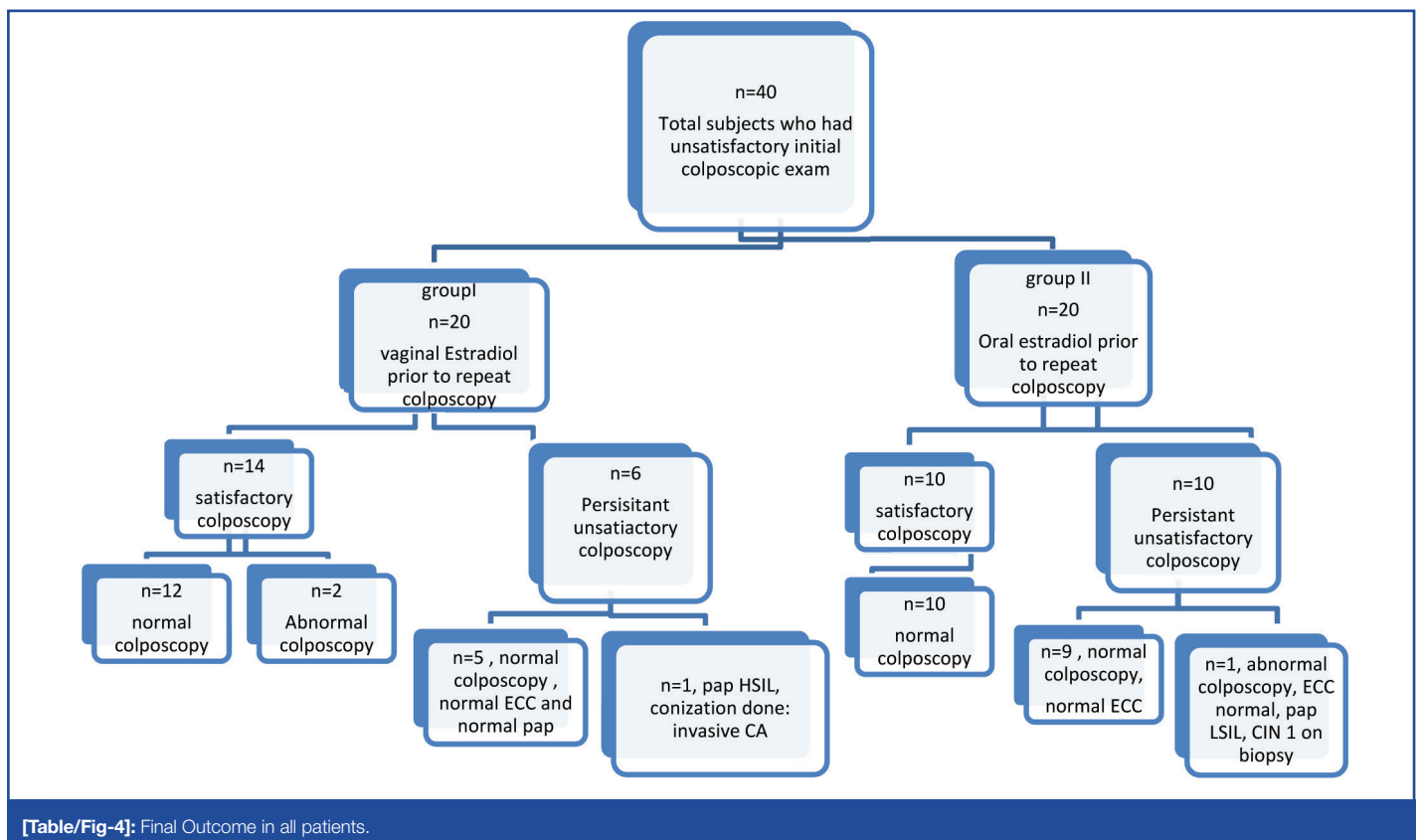
[Table/Fig-1]: Distribution of unsatisfactory colposcopy in patients screened for the study.

Characteristics	Variables	Group-I (vaginal estradiol) n (%)	Group- II (Oral Estradiol) n (%)	p-value
Age distribution (in years)	≤30	2(10)	3(15)	0.8
	31-40	5(25)	5(25)	
	41-50	4(20)	3(15)	
	≥50	9(45)	9(45)	
Parity	≤1	1(5)	1(5)	0.9
	2	4(20)	6(30)	
	≥3	15(75)	13(65)	
Drug efficacy	Satisfactory colposcopy on repeat exam	14(70)	10(50)	0.19
	Unsatisfactory colposcopy on repeat exam	6(30)	10(50)	
Drug safety	All adverse effects	4(20)	5(25)	0.8
	Nausea	1(5)	4(20)	0.8
	Discharge per vaginum	3(15)	1(5)	0.06

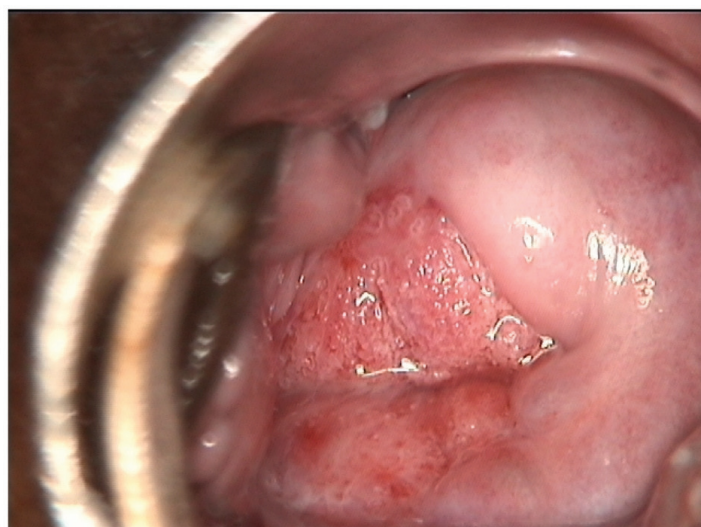
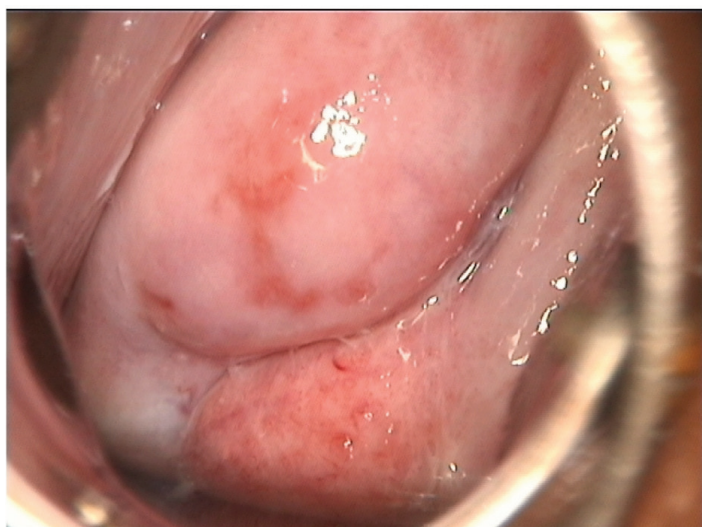
[Table/Fig-2]: Patient characteristics, drug efficacy and adverse effects for two study groups.

Invisibility of transformation zone	No. of responders/total no. of patients : Group-I	No. of responders/total no. of patients : Group-II
On anterior lip	3/4(75%)	3/4(75%)
On Posterior Lip	4/4(100%)	2/6(33%)
Both lips	7/12(58%)	5/10(50%)
	p=0.2(Chi-Square Test)	p=0.4(Chi-Square Test)

[Table/Fig-3]: Correlation between site of unsatisfactory colposcopy and response to the drug in two groups



[Table/Fig-4]: Final Outcome in all patients.



Table/Fig-5: A figure showing partial visualization of transformation zone on colposcopy. **Table/Fig-6:** Complete visualization of transformation zone after administrating medication.

rate with estrogen was 65% versus 10% with the placebo ($p < 0.05$). In a separate non-randomized study by Prednivilli et al., 100 µg of oral estradiol administered for 5 consecutive days allowed complete visualization of TZ in 16 out of 25 patients with previously non-visualized TZ (response rate of 64%) [8]. Nausea was the only reported adverse effect.

There have been few studies elucidating the efficacy of intravaginal estrogen administration in improving the visualization of TZ on colposcopy. Recently, Piccolo et al., studied 178 postmenopausal women who had partial or non-visualized TZ during colposcopy [9], of which 3-month intravaginal administration of estrogen resulted in a complete visualization of TZ in 73% of the patients during the follow-up colposcopy.

In another study by Richards et al., 54 patients with abnormal cervicovaginal smears with hypo-estrogenic state (postmenopausal or amenorrhagic postnatal) underwent colposcopic examination [10]. All of them had partial or non-visualized TZ and were treated with local estrogen cream applied twice a week for 6 weeks. A 32 of them had complete visualization of the TZ on follow up colposcopy. In addition, 40 patients had a normal pap smear after therapy. The authors concluded that the use of vaginal estrogen cream improves the visualization of transformation zone in colposcopy and also the accuracy of prediction of true pre-invasive disease.

In a recent randomized controlled trial conducted by us [4], a single dose of 200µg vaginal misoprostol was successful in 70% of patients in overcoming the non-visualization of TZ during colposcopy as compared to 82% with the administration of 50µg vaginal estradiol for 7 consecutive days. However, this difference was statistically non-significant.

In the present study, the efficacy of vaginal estradiol was 70% as compared to 50% with oral estradiol. Different dosages of estrogens have been used for a varying duration in different studies [4,7-10]. No single regimen has been found to be significantly superior to the others in improving the visualization of the TZ. In the present study, administration of the minimum possible dose of estradiol was done in order to minimize the incidence of side effects.

It is important to note that estradiol enabled complete visualization of the TZ in majority of the subjects, irrespective of route of administration [Table/Fig-5,6]. There is strong evidence that gonadal steroid hormones are important in regulation of cervical ripening [11]. It has been demonstrated that estrogens stimulate collagen degradation invitro, an effect that is blocked by progesterone [11]. Women with placental sulphatase deficiency have low levels of estrogen and do not undergo cervical ripening at term [10]. It is recognized that both oral contraceptive pills and

pregnancy are associated with cervical eversion whereby columnar epithelium becomes visible on ectocervix [12,13].

Another important observation in our study was that the response to the drug varied with the site of non-visualization of transformation zone colposcopy. In Group I, patients with invisibility of transformation zone on posterior lip responded to a greater extent as compared to those with invisibility of transformation zone on anterior lip. Whereas, in Group II, subjects with involvement of anterior lip responded better as compared to those with involvement on posterior lip [Table/Fig-3]. This observation is along the similar lines in a different study by us [4] in which 65% of the patients with non-visualized posterior lip responded to 200µg of misoprostol as compared to 94% of the patients with involvement of anterior lip (p -value=0.05). In the same study, 81% of patients treated with 50µg of vaginal estradiol (for 7 days) with non-visualized anterior lip responded as compared to 84% patients with involvement on posterior lip ($p=0.5$). The reason for the difference in response of the anterior and posterior lips of the cervix to estrogens is unknown. Major adverse effects of the estrogen therapy were nausea and vaginal discharge, however, the difference was statistically non-significant [Table/Fig-2]. Response was comparable in premenopausal and postmenopausal women with the 2 drug regimens. Thus, menopausal status did not have any effect on response to the treatment.

LIMITATION

The present study could not be blinded and sample size was relatively small despite being statistically sufficient. More randomized trials with larger sample size are needed to confirm the findings.

CONCLUSION

In conclusion, both vaginal and oral estradiol have comparable efficacy in overcoming the partial or non-visualization of transformation zone on colposcopy with similar incidence of adverse effects.

REFERENCES

- [1] Sankarnarayan R, Budukh A, Rajkumar R. Effective screening programs for cervical cancer in low and middle income developing countries. *Bull World Health Organ.* 2001;79:954-62.
- [2] Singer A, Walker P. What is the optimal treatment of cervical malignancy? *Br J Obstet Gynecol.* 1982;89:335-37.
- [3] Rochelson B, Krumholz BA. The "unsatisfactory" colposcopic examination. *J Reprod Med.* 1983;28(2):131-36.
- [4] Makkar B, Batra S, Gandhi G, Zutshi V, Goswami D. Vaginal misoprostol versus vaginal estradiol in overcoming unsatisfactory colposcopy. *Gynecol Obstet Invest.* 2014;77(3):176-79.

- [5] 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(2):115-20.
- [6] Bornstein J, Bentley J, Bozse Girardi F. Colposcopy terminology of International Federation of Cervical Pathology and Colposcopy. *Obstet Gynecol.* 2012;120:166-72.
- [7] Saunders N, Anderson D, Gilbert L, Sharp F. Unsatisfactory colposcopy and the response to orally administered oestrogen: a randomized double blind placebo controlled trial. *Br J Obstet Gynecol.* 1990;97(8):731-33.
- [8] Predniviili 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 Gynecol.* 1986;93(5):508-11.
- [9] Piccoli R, Mandato VD, Lavitola G, Acunzo G, Bifulco G, Tommaselli GA, et al. Atypical squamous cells and low squamous intraepithelial lesions in postmenopausal women: implications for management. *Eur J Obstet Gynecol Reprod Biol.* 2008;140(2):269-74.
- [10] Richards A, Dalrymple C. Abnormal cervicovaginal cytology, unsatisfactory colposcopy and the use of vaginal estrogen cream: an observational study of clinical outcomes for women in Low estrogen states. *J Obstet Gynecol Res.* 2015;41(3):440-44.
- [11] France JT, Seddon RJ, Liggins GC. A study of pregnancy with low estrogen production due to placental sulfatase deficiency. *J Clin Endocrinol Metab.* 1973;36:1-9.
- [12] Cobbleson M. Colposcopic study of cervix during pregnancy. *J Obs Gyn Br cwith.* 1996;73:575-81.
- [13] Mingeot R, Fievez C. Endocervical changes with the use of synthetic steroids. *Obstet Gynecol.* 1974;44(1):53-59.

PARTICULARS OF CONTRIBUTORS:

1. Consultant, Karan Hospital, Bijnour, Uttarpradesh, India.
2. Clinical Associate, Fortis Hospital, Shalimar Bagh, New Delhi, India.
3. Head of Department, Department of Obstetrics and Gynaecology, Hamdard Institute of Research and Medical Sciences, New Delhi, India.
4. Professor, Department of Obstetrics and Gynaecology, Maulana Azad Medical College, New Delhi, India.
5. Professor, Department of Obstetrics and Gynaecology, Maulana Azad Medical College, New Delhi, India.
6. Senior Specialist, Department of Obstetrics and Gynaecology, Safdarjung Hospital, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Binni Makkar,
2643, Hudson Lane, GTB Nagar, New Delhi-110009, India.
E-mail: binnimkr@gmail.com

Date of Submission: **Feb 12, 2016**Date of Peer Review: **Mar 31, 2016**Date of Acceptance: **May 24, 2016**Date of Publishing: **Jul 01, 2016****FINANCIAL OR OTHER COMPETING INTERESTS:** None.