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Comparison of Estradiol and Misoprostol in Transformation Zone Visibility in Colposcopy

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ABSTRACT

Background & Objective: Estradiol and misoprostol have been used for the enhancement of transformation zone (TZ) visibility in vaginal colposcopy. However, no consensus has been reached on the superiority of one medication over the other. This study aimed to compare the efficacy of estradiol and misoprostol for the enhancement of TZ visibility in vaginal colposcopy of premenopausal and postmenopausal women.

Materials & Methods: In this clinical trial, 78 patients with unsatisfactory colposcopy were randomly divided into three groups. Group 1 (*n*=25) received 25 µg of vaginal estradiol for 14 days prior to colposcopy. Group 2 (*n*=27) received 400 µg of misoprostol 12 h prior to colposcopy. Group 3 (*n*=26) served as the control group and did not receive any medication. Visibility of the TZ, age, body mass index (BMI), history of vaginal delivery, history of sexually transmitted diseases, history of human papillomavirus (HPV), the reason for colposcopy, and drug-related side effects were compared among the three groups and also between premenopausal and postmenopausal women. Data were analyzed using analysis of variance (ANOVA), Kruskal-Wallis, Chi-square, and Fisher's exact tests.

Results: The percentage of TZ visibility was 72%, 55.6%, and 26.9% in the estradiol, misoprostol, and control groups, respectively (*P*=0.005). These values were 70%, 33.3%, and 0%, respectively, in postmenopausal women (*P*=0.043) and 60%, 72.7%, and 33.3%, respectively, in premenopausal women (*P*=0.152). Regarding drug-related side effects, there was no statistically significant difference between the three groups (*P*=0.374).

Conclusion: Estradiol was significantly superior to misoprostol for the enhancement of TZ visibility, particularly in postmenopausal women, with no difference regarding side effects.

Keywords: Estradiol; Misoprostol; Colposcopy; Transformation Zone; Visibility

Introduction

Cervical cancer is the third most common cancer and the fourth most common cause of cancer-related mortality in women worldwide, with about 15 million new cases and 9 million deaths annually **(1-3)**. Cervical cancer is often asymptomatic in the early stages. Thus, cervical cancer screening is important for early detection of premalignant lesions **(4-6)**.

Colposcopy plays a fundamental role in the detection and management of cervical neoplasms and is an important diagnostic tool for the evaluation of patients with abnormal Pap smears **(7, 8)**. The transformation zone (TZ) is not clearly visible in approximately 10% to 20% of patients during colposcopy, which is referred to as unsatisfactory colposcopy **(9, 10)**. Such patients often require more invasive procedures, such as electrosurgery or conization, which may lead to bleeding, infection, cervical insufficiency, and premature delivery **(11)**. Several methods are employed to minimize the number of unsatisfactory colposcopies, such as endocervical speculum, hygroscopic cervical dilators, and oral or vaginal administration of estrogen or misoprostol **(12-14)**.

Misoprostol is a prostaglandin E1 analog, which was first used for the treatment of gastric ulcers. At present, it is extensively used in obstetrics and gynecology due to its optimal efficacy for cervical softening **(15, 16)**. Its advantages include thermal stability, low cost, and easy administration. It is available in different forms and doses (200, 400, 800, and 1000 µg), which can be administered orally, vaginally, or rectally. It is also commonly used for cervical softening prior to hysteroscopy **(17-20)**.

Two meta-analyses demonstrated that misoprostol, compared to placebo, decreased the complications of hysteroscopy and the need for cervical dilation. They also showed that vaginal administration of 200-400 µg of misoprostol was a simple, effective method for cervical softening in all postmenopausal and premenopausal women **(21, 22)**. Although the favorable efficacy of misoprostol for reducing the need for cervical dilation has been confirmed in premenopausal women, its efficacy for postmenopausal women is still unclear, and further studies on postmenopausal and non-menopausal women are required to better understand this topic.

The excellent outcomes of misoprostol in premen-opausal women have suggested the interaction of sex hormones with misoprostol. Treatment with estradiol prior to misoprostol may yield a synergistic effect. Considering the gap of information on this topic, this study aimed to compare the efficacy of estradiol and misoprostol for the enhancement of TZ visibility in vaginal colposcopy of premenopausal and postmen-opausal women.

Materials and Methods

This randomized clinical trial was conducted on 78 patients with unsatisfactory colposcopy presenting to Moheb-Yas and Imam Khomeini Hospitals in Tehran. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1396.4542). All patients were briefed about the study and signed written informed consent forms before enrollment.

Patients who were candidates for colposcopy were included in this study, and patients with allergy to the medications or with conditions contraindicating their administration were excluded. The patients were randomly divided into three groups using a block randomization software package.

Group 1 (n=25) received 25 µg of vaginal estradiol (Abureyhan Pharmaceuticals, Tehran, Iran) for 14 days prior to colposcopy. Group 2 (n=27) received 400 µg of misoprostol (Samisaz, Tehran, Iran) 12 h prior to colposcopy. Group 3 (n=26) served as the control group and did not receive any medication.

Visibility of the TZ, age, body mass index (BMI), history of vaginal delivery, history of sexually transmitted diseases, history of human papillomavirus (HPV), the reason for colposcopy, and drug-related side effects were compared among the three groups and also between premenopausal and postmenopausal women.

Quantitative variables were reported as means and SDs, while qualitative variables were reported as percentages. The normal distribution of data was evaluated using the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were compared using analysis of variance (ANOVA), while those with non-normal distribution were compared using the Kruskal-Wallis test. Qualitative variables were compared using the chi-square test or Fisher's exact test. All statistical analyses were carried out using SPSS 22 (SPSS Inc., Chicago, Ill., USA) and SAS 9.1 at 0.05 level of significance.

Results

Table 1 presents the demographic and general information of patients. There was no statistically significant difference between the three groups regarding age (menopausal, premenopausal, or postmenopausal; P=0.333), BMI (P=0.988), prevalence of HPV+ cases (P=0.354), frequency of multi-partner cases (P=0.085), drug-related side effects (P=0.374), or the reasons for colposcopy (HPV+, bleeding during intercourse, abnormal cervix, abnormal Pap smear, and so on; P=0.708).

There was a statistically significant difference between the three groups regarding the mean number of gravidity (P=0.042). The post hoc test showed that only the difference between the placebo and estradiol groups was significant, and the mean number of gravidity in the estradiol group was significantly higher than that in the placebo group (P=0.044). Also, there was a statistically significant difference between the three groups regarding the type of delivery (P=0.029).

Table 2 shows the percentage of TZ visibility in the three groups. As shown, there was a statistically significant difference between the three groups in this respect (P=0.005), and the estradiol group showed maximum TZ visibility. Thus, binary logistic regression was performed, which revealed that the odds of TZ visibility in the estradiol group were significantly higher than those in the placebo group by 6.9 times (OR=6.98; 95% CI, 2.04-23.88; P=0.002). The odds of TZ visibility in the misoprostol group were also significantly higher than those in the placebo group by 3.3 times (OR=3.39; 95% CI, 1.07-10.74; P=0.038).

The separate assessment of postmenopausal and premenopausal women revealed a significant difference in the percentage of TZ visibility between the three groups in postmenopausal women (P=0.042), and the highest percentage of visibility was observed in the estradiol group. However, this difference was not significant between the three groups in premenopausal women (P=0.152).

Table 1. Demographic and general information of patients in the three groups

Characteristic	Estradiol (n=25)	Misoprostol (n=27)	Control (n=26)	P-value
Age group				
Menopausal	10(40.0%)	9.(33.3%)	4(15.4%)	0.333
Premenopausal	10(40.0%)	11(40%)	12(46.2%)	
Other	5(20.0%)	7(25.9%)	10(38.5%)	
BMI				
< 25	12(48.0%)	13(48.1%)	14(53.8%)	0.988
25-30	8(32.0%)	9(33.3%)	7(26.9%)	
>30	5(20.0%)	5(18.5%)	5(19.2%)	
Number of gravidity	2.88±1.42	2.15±1.85	1.69±1.66	0.042
Type of delivery				0.008
Normal vaginal	17(68.0%)	12(44.4%)	9(34.6%)	
Cesarean section	3(12.0%)	5(18.5%)	3(11.5%)	
Prevalence of HPV +	4(16.0%)	9.(33.3%)	7(26.9%)	0.354
Multi-partner cases	0(0.0%)	5(18.5%)	4(15.4%)	0.069
Reason for colposcopy				
HPV (+)	5(20.0%)	8(29.6%)	8(30.8%)	0.748
Bleeding during intercourse	6(24.0%)	2(7.4%)	3(11.5%)	
Abnormal cervix	4(16.0%)	5(18.5%)	4(15.4%)	
Abnormal Pap smear	9(36.0%)	9.(33.3%)	7(26.9%)	
Other	1(4.0%)	3(11.1%)	4(15.4%)	

Table 2. Percentage of visibility of the transformation zone in the three groups in premenopausal and postmenopausal women

Characteristic	Estradiol (n=25)	Misoprostol (n=27)	Control (n=26)	P-value
Percentage of visibility	18(72.0%)	15(55.6%)	7(26.9%)	0.005
Postmenopausal patients	7(70.0%)	(33.3%)3	0(0.0%)	0.043
Premenopausal patients	6(60%)	8(72.7%)	4(33.3%)	0.152
Drug-related side effects	1(4.0%)	2(7.4%)	0(0.0%)	0.649

Discussion

The concept of transformation of glandular epithelium to squamous epithelium, also known as squamous metaplasia, is the basis for a correct understanding of the pathogenesis of squamous cell carcinoma of the cervix. The distribution of cervical cancer precursors has a direct correlation with the extent of the transformed metaplastic epithelium, which is referred to as TZ. Thus, precise assessment of this region is critical for early detection of cervical cancer; accordingly, colposcopy is indicated for this purpose. Nonetheless, complete detailed observation of TZ is problematic in some cases and requires the administration of some medications to enhance TZ visibility. Estradiol and misoprostol have been used for the enhancement of TZ visibility in vaginal colposcopy. However, no consensus has been reached on the superiority of one medication over the other. Thus, this study compared the efficacy of estradiol and misoprostol for the enhancement of TZ visibility in vaginal colposcopy of premenopausal and postmenopausal women.

The results showed that estradiol was significantly superior to misoprostol for the enhancement of TZ visibility, particularly in postmenopausal women, and the two medications had no significant difference regarding drug-related side effects; however, the frequency of drug-related side effects was slightly—but not significantly—higher in the misoprostol group.

Beniwal *et al*. **(12)** reported that vaginal application of 25-µg estradiol improved TZ visibility by 70%, which was close to our obtained value. Aggarwal *et al*. **(23)** reported that TZ visibility was significantly higher in the misoprostol group than in the placebo group. Although this result was expected, the visibility enhancement was 78.9% in their study, which was higher than our obtained value (55%). This difference may be attributed to the differences in sample size.

In contrast to our findings, Pergialiotis *et al*. **(24)** reported that treatment with misoprostol enhanced the TZ visibility during colposcopy by 10.2 times (24). Further, Makkar *et al*. **(25)** reported successful colposcopy rates of 70.8% and 82.6% in misoprostol and estradiol groups, respectively. Their findings supported the superiority of estradiol for this purpose, which was in line with our findings. However, this difference did not reach statistical significance in their study. The rate of drug-related side effects in their study was 41.6% in the misoprostol group and 13% in the estradiol group; this difference was statistically significant. In our study, no significant difference was found in the frequency of drug-related side effects between the three groups. Thanapprapasr *et al*. **(22)** reported that the success rate of colposcopy following the administration of misoprostol was 20%, which was much lower than the value reported in our study. Discrepancies in the results of studies can be due to variations in study design, sample size, treatment protocols with regard to drug dosages and duration of administration, and the brand of medication **(22)**.

This study had some limitations, which should be taken into account when interpreting the results, such as small sample size and significant differences between the three groups in some factors such as the number of gravity and multi-partner cases, which can have confounding effects on the results.

Conclusion

Estradiol was significantly superior to misoprostol for the enhancement of TZ visibility, particularly in postmenopausal women. Further, no significant difference was found between the two medications regarding the frequency of drug-related side effects.

Acknowledgments

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1396.4542).

Conflict of Interest

There is no conflict of interest to declare.

Authors Contribution

Study concept and design: Elham Shirali; Acquisition of data: Shaghayegh Nowroozi; Analysis and interpretation of data: Elham Shirali, Sara Ramhormozian; Drafting of the manuscript: Fariba Yarandi; Critical revision of the manuscript for important intellectual content: Elham Shirali, Sara Ramhormozian; Statistical analysis: Narges Zamani; Administrative, technical, and material support: Sara Ramhormozian; Study supervision: Mitra Modares Gilani

References

1. Shrestha AD, Neupane D, Vedsted P, Kallestrup P. Cervical Cancer Prevalence, Incidence and Mortality in Low and Middle Income Countries: A Systematic Review. Asian Pac J Cancer Prev. 2018;19(2):319-24. [DOI:10.1111/ecc.13207] [PMID]
2. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health. 2020;8(2): e191-e203. [DOI:10.1016/S2214-109X(19)30482-6]
3. Vu M, Yu J, Awolude OA, Chuang L. Cervical cancer worldwide. Current problems in cancer. 2018 Sep 1;42(5):457-65. [DOI:10.1016/j.currproblcancer.2018.06.003] [PMID]
4. Zhang S, McNamara M, Batur P. Cervical Cancer screening: What's new? Updates for the busy clinician. Am J Med. 2018;131(6):702-e1. [DOI:10.1016/j.amjmed.2018.01.020] [PMID]
5. Pimple SA, Mishra GA. Global strategies for cervical cancer prevention and screening. Minerva Ginecol. 2019;71(4):313-20. [DOI:10.23736/S0026-4784.19.04397-1]
6. Bhatla N, Singhal S. Primary HPV screening for cervical cancer. Best Pract Res Clin Obstet Gynaecol. 2020;65:98-108 . [DOI:10.1016/j.bpobgyn.2020.02.008] [PMID]
7. Hirai CM, Kaneshiro B, Hiraoka MK. The Effect of the 2012 ASCCP Consensus Guideline for Abnormal Cervical Cytology on Resident

Colposcopy Training. Hawaii J Med Public Health. 2018;77(1):3-6.

8. Burness JV, Schroeder JM, Warren JB. Cervical Colposcopy: Indications and Risk Assessment. Am Fam Physician. 2020;102(1):39-48. PMIid: 32603071.

9. Manley KM, Simms RA, Platt S, Patel A, Bahl R. Unsatisfactory colposcopy: clinical decision-making in conditions of uncertainty. BMC Med Inform Decis Mak. 2017;17(1):125. [DOI:10.1186/s12911-017-0516-3] [PMID] [PMCID]

10. Chevreau J, Carcopino X, Foulon A, Preaubert L, Lanta-Delmas S, Sergent F, Gondry J. Risk factors for unsatisfactory colposcopy after large loop excision of the transformation zone: The results of a four-year multicenter prospective study. Eur J Obstet Gynecol Reprod Biol. 2019;240:156-160. [DOI:10.1016/j.ejogrb.2019.07.001] [PMID]

11. Ciavattini A, Delli Carpini G, Moriconi L, Clemente N, Montik N, De Vincenzo R, Del Fabro A, Buttignol M, Ricci C, Moro F, Sopracordevole F. Effect of age and cone dimensions on cervical regeneration: an Italian multicentric prospective observational study. BMJ Open. 2018;8(3):e020675. [DOI:10.1136/bmjopen-2017-020675] [PMID] [PMCID]

12. Beniwal S, Makkar B, Batra S, Gandhi G, Goswami D, Zutshi V. Comparison of Vaginal versus Oral Estradiol Administration in Improving the Visualization of Transformation Zone (TZ) during Colposcopy. J Clin Diagn Res. 2016;10(7):QC18-21. [DOI:10.7860/JCDR/2016/19492.8201] [PMID] [PMCID]

13. Vallikad E, Siddartha PT, Kulkarni KA, Firtion C, Keswarpu P, Vajinepalli P, et al. Intra and Inter-Observer Variability of Transformation Zone Assessment in Colposcopy: A Qualitative and Quantitative Study. J Clin Diagn Res. 2017;11(1): XC04. [DOI:10.7860/JCDR/2017/21943.9168] [PMID] [PMCID]

14. Ayensu-Coker L, Sanchez J, Zurawin R, Dietrich JE. Use of misoprostol for management of unsatisfactory colposcopy in the adolescent: a case report and review of the literature. J Pediatr Adolesc Gynecol. 2009;22(5):e139. [DOI:10.1016/j.jpag.2008.12.001] [PMID]

15. Allen R, O'Brien BM. Uses of misoprostol in obstetrics and gynecology. Rev Obstet Gynecol. 2009 Summer;2(3):159-68.

16. Chong YS, Su LL, Arulkumaran S. Misoprostol: a quarter century of use, abuse, and creative misuse. Obstet Gynecol Surv. 2004;59(2):128-40. [DOI:10.1097/01.OGX.0000109168.83489.66] [PMID]

17. Nakano FY, Yela DA, Pinto JPL, Riegas T, Benetti-Pinto CL, Pedro AO, et al. Efficacy of misoprostol before diagnostic hysteroscopy in postmenopausal women: a randomized clinical trial. Menopause. 2018;25(7):789-94. [DOI:10.1097/GME.0000000000001074] [PMID]

18. Polyzos NP, Zavos A, Valachis A, Dragamestianos C, Blockeel C, Stoop D, et al. Misoprostol prior to hysteroscopy in premenopausal and postmenopausal women. A systematic review and meta-analysis. Hum Reprod Update. 2012;18(4):393-404. [DOI:10.1093/humupd/dms014] [PMID]

19. Al-Fozan H, Firwana B, Al Kadri H, Hassan S, Tulandi T. Preoperative ripening of the cervix before operative hysteroscopy. Cochrane Database Syst Rev. 2015;(4):CD005998. [DOI:10.1002/14651858.CD005998.pub2] [PMID]

20. Casadei L, Piccolo E, Manicuti C, Cardinale S, Collamarini M, Piccione E. Role of vaginal estradiol pretreatment combined with vaginal misoprostol for cervical ripening before operative hysteroscopy in postmenopausal women. Obstet Gynecol Sci. 2016 May;59(3):220-6. [DOI:10.5468/ogs.2016.59.3.220] [PMID] [PMCID]

21. Hwang JY, Song SH. Optimal Dose of Vaginal Misoprostol for Cervical Ripening before Hysteroscopy: A Randomized Double-Blind Study. J Minim Invasive Gynecol. 2018;25(6):1031-4. [DOI:10.1016/j.jmig.2018.01.022] [PMID]

22. Thanapprapasr D, Wilailak S, Ayudhya NI, Lertkhachonsuk AA, Likittanasombut P, Chittithaworn S, Charakorn C, Weerakiet S. Can vaginal misoprostol effectively increase rate of a satisfactory colposcopy? A randomized double-blind placebo-controlled trial. Jpn J Clin Oncol. 2010;40(3):203-7. [DOI:10.1093/jjco/hyp140] [PMID]

23. 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. [DOI:10.1159/000093623] [PMID]

24. Pergialiotis V, Vlachos DE, Pitsouni E, Perrea D, Vlachos GD. Vaginal Misoprostol for Overcoming Inadequate Colposcopies: A Meta-analysis of Randomized Controlled Trials. J Low Genit Tract Dis. 2015;19(3):257-61. [DOI:10.1097/LGT.0000000000000066] [PMID]

25. 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):176-9. [DOI:10.1159/000358391] [PMID]

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