Journal of Midwifery & Reproductive Health

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Clinical Improvement, Disease recurrence, and Patient Satisfaction Following Treatment with Vaginal Effervescent Tablets of Tranexamic Acid and Cryotherapy in Patients with Symptomatic Cervical Ectropions: A Randomized Controlled Trial

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ARTICLE INFO

Article type:
Original article

Article History:
Received: 30-Nov-2022
Accepted: 27-Feb-2023

Key words:
Tranexamic Acid
Cryotherapy
Patient Satisfaction
Randomized Controlled Trial

ABSTRACT

Background & aim: Cervical ectropion refers to a condition in which the cylindrical epithelium of the endocervix extends towards the ectocervix. The present study was conducted to compare clinical improvement, disease recurrence, and patient satisfaction following treatment with vaginal effervescent tablets of tranexamic acid and cryotherapy in patients with symptomatic cervical ectropions.

Methods: This randomized clinical trial was conducted on 92 women with symptomatic cervical ectropions from March 2021 until September 2022 at Ayatollah Mousavi Hospital in Zanjan. Sampling was done at first step by convenience sampling, and then randomly assigning the sample to two groups: an intervention group receiving 400 mg of vaginal effervescent tranexamic acid tablets for 10 days and a comparison group with cryotherapy. At the end of the third month of the intervention, the rate of clinical improvement, disease recurrence, and patient satisfaction were evaluated in both groups. Data analysis was performed by SPSS software (version 22) using Chi-square and Fisher's exact tests.

Results: At the end of the intervention, 97.72% and 93.18% of the participants reported improvement in clinical symptoms following tranexamic acid and cryotherapy, respectively. There was no statistically significant difference between the two groups in terms of clinical improvement (P = 0.31), disease recurrence (P = 0.64), and patient satisfaction (P = 0.57).

Conclusion: Considering the similar effectiveness of tranexamic acid and cryotherapy in improving the clinical symptoms of patients, this method can be a suitable alternative to cryotherapy.

Please cite this paper as:
Hekmatfar F, Tofighi Sh, Gholami H, Tavakolizadeh M, Haghighi M. Clinical Improvement, Patient Satisfaction, and disease recurrent Following Treatment with Vaginal Effervescent Tablets of Tranexamic Acid and Cryotherapy in Patients with Symptomatic Cervical Ectropions: A Randomized Controlled Trial. Journal of Midwifery and Reproductive Health. 2023; 11(4): 3910-3918. DOI: 10.22038/JMRH.2023.69306.2036

Introduction

Cervical ectropion refers to a condition in which the cylindrical epithelium of endocervix extends towards ectocervix and leads to the placement of the T-zone in the vaginal environment (1). It is said that this condition is a physiological condition, the location of which is influenced by sex hormones, so the use of contraceptive pills, puberty, pregnancy, and childbirth can lead to changes in the location of

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this area towards the ectocervix. Different studies have reported the prevalence of 17 to 50% of cervical ectropions in women of reproductive age (1). The results of a study in Libya show that 54.9% of women who used contraceptive pills and copper IUDs had cervical ectropion (2). Cervical ectropions are also seen in 80% of sexually active adolescents (1).

Cylindrical epithelium cells are thinner and more fragile than squamous epithelium, and their blood vessels are visible, which can lead to the red appearance of the ectopic area during vaginal examination. On the other hand, the thin and fragile blood vessels of this area provide easy access to the blood and lymphatic system for many microorganisms, reduce the mucous barriers for sexually transmitted infections, and play an important role in the secondary transmission of infection (3). Epidemiological studies show that cervical ectopy can increase the risk of some sexually transmitted diseases such as Chlamydia trachomatis, Human Papillomavirus (HPV), Neisseria gonorrhoeae, Cytomegalovirus, and AIDS (3-5). Although cervical ectopies are mostly asymptomatic, they can be associated with symptoms such as leucorrhea, pelvic pain, intermenstrual spotting, recurrent cervicitis, dyspareunia, and spotting after intercourse (1).

There is no consensus among physicians about whether cervical ectropions are a physiological state or a condition that needs treatment. Some physicians believe that uterine ectropions are not only caused by hormonal changes, but trauma and inflammation can also play an important role in the pathogenesis of this disease (6). Inflammatory ectropions are associated with degeneration and necrosis of squamous epithelium of the cervix along with infiltration of a large number of inflammatory cells. In the smear of superficial, middle, and basal cells, degenerated cells, necrotic and mild dyskaryotic cells along with many neutrophils can be seen, which indicates the inflammatory nature of ectropions (7). On the other hand, macroscopically, it is difficult to distinguish it from cervical intraepithelial neoplasia (CIN), so examination of cervical smear is recommended for all ectropion lesions (6).

Nowadays, many medical professionals recommend using different methods for reasons such as relief of symptoms of chronic cervicitis, treatment of recurrent cervicitis, and prevention and treatment of CIN, especially in low-income countries that do not have the necessary infrastructure for triage, management, and treatment of cancer. They also recommend using different methods to eliminate the ectopic area (5,8).

Various studies support the use of different treatment methods such as electrocautery, cryotherapy, laser, focused ultrasound, microwaves, autologous platelet-rich plasma, and drugs such as alpha interferon suppositories, polydeoxyribonucleotide, and boric acid to destroy the ectopic area (9-11).

Cryotherapy is considered one of the most effective treatment methods for cervical ectropions. In this method, prep cryo is placed on the ectopic area for two minutes with direct surface contact to freeze the desired area. At the freezing temperature, water crystallizes in the extracellular spaces, which in turn leads to cell dehydration, which is called "solution-effect injury". Freezing the area by creating intracellular hyperosmotic conditions leads to cell injury in the desired area (12-13). Despite the high effectiveness of this method, the need for necessary equipment and a trained person limits its use. On the other hand, the use of this method in recurrent and benign ectropions is doubtful (14-15).

Recently, there have been limited studies that support the role of tranexamic acid in the treatment of uterine ectropions. Although the mechanism of action of this drug is still not clear, it seems that tranexamic acid plays this role by inhibiting angiogenesis and inflammatory factors (16-18).

Since the high prevalence of uterine ectropions, makes it very important to choose a suitable, cost-effective and easy to use treatment, the present clinical trial was performed to compare the clinical improvement, disease recurrence, and patient satisfaction in two groups of women with symptomatic ectropion treated with cryotherapy and vaginal effervescent tablets of tranexamic acid.

Materials and Methods

This randomized clinical trial, which is an equivalence trial was performed from March 2021 until September 2022 on 92 women with

symptomatic cervical ectropion who had been referred to the gynecology clinic of Ayatollah Mousavi Hospital in Zanjan, Iran. The research ethics committee of Zanjan University of Medical Sciences has approved the study (IR.ZUMS.REC.1400.428). Also, this study has been registered in the Iranian Registry of Clinical Trials (IRCT20220115053719N1).

After the detailed explanation of the objectives of the study, written informed consent and oral consent were obtained from all participants, and they were assured their information would remain confidential and they could withdraw from the study whenever they wished.

Inclusion criteria were the age range of 20 to 45 years, observation of cervical ectropion during vaginal examination with a speculum, and presence of ectropion symptoms (such as leucorrhoea, pelvic pain, abdominal pain, and spotting after sexual intercourse). Exclusion criteria were diagnosis of any type of dysplasia or neoplasia in cervix cytology, infection with HPV and other sexually transmitted infections, pregnancy, and unwillingness to continue the study.

The sample size was estimated at 42 subjects in each group based on the Neha Garg's study (16), and considering a 10% dropout rate ,95% confidence interval, and 85% test power, it increased to 46 participants in each group. There were two dropouts in the group treated with tranexamic acid (one case of COVID-19 infection and one case of unwillingness to participate in the study) and two dropouts in the cryotherapy group due to a change in the place of residence (Figure 1).

For sampling, at first, qualified women who met the inclusion criteria and were diagnosed with cervical ectropion during vaginal examination with speculum were included in the study. Sampling was done using the convenience method. This study used block randomization. This method was used to balance the number of samples assigned to each group. For concealment, random allocation concealment was used, so that the opinion of the researcher or the people participating in the research has no effect on their placement in the intervention or control group. The participants were randomly assigned to intervention (A) and control (B) groups using permutation blocks of four (including 2 cases treated with cryotherapy and 2 cases treated with tranexamic acid). The status of four patients was determined by selecting each block using a table of random numbers.

The patients of the intervention group were first placed in the lithotomy position; the vaginal secretions and mucus on the cervix were removed using a cotton swab. Then, 500 mg of tranexamic acid in the form of a vaginal effervescent tablet was placed in the cervix area using an applicator. Then the patient was asked to remain in the same position for 15 minutes. The method of taking the medicine was explained precisely to the patient and the required amount for ten days was given to the patient. They were asked to refer for weekly visits in the first month and then monthly for three months. The results and local and systemic side effects were recorded by the researcher based on repeated examinations.

In this study, for the first time, a vaginal effervescent tablet containing 500 mg of tranexamic acid and other permitted and common pharmaceutical excipients such as Avicel 102, citric acid, sodium bicarbonate, talc, and aerosol was formulated and manufactured by a simple direct pressing method in Amin Pharmaceutical Company. If the desired therapeutic effect is achieved,, a new form of this drug can be introduced to the Iranian pharmaceutical market. . The safety of this drug has been approved by the FDA (19).

The patients in the control group underwent cryotherapy, and the cryotherapy probe was selected based on the size and location of the erosion. Cryotherapy using liquid nitrogen/carbon dioxide at zero temperature for 3 to 5 minutes with direct surface contact was placed on the lesion until a 5 mm sphere was seen. It was explained to the patients that they may have bloody discharge for 4-5 days after the procedure.

To check the rate of clinical recurrence and clinical improvement of symptoms through vaginal examination with a speculum before starting the treatment, an image of the cervix was taken and compared with the current view.

There was no standard tool for this measurement, which could increase the risk of bias.

Clinical satisfaction was measured using a question based on the Likert scale (no satisfaction, low satisfaction, moderate satisfaction, good satisfaction, and complete satisfaction) at the end of the intervention. This question was scored between 1 (no satisfaction) and 5 (complete satisfaction).

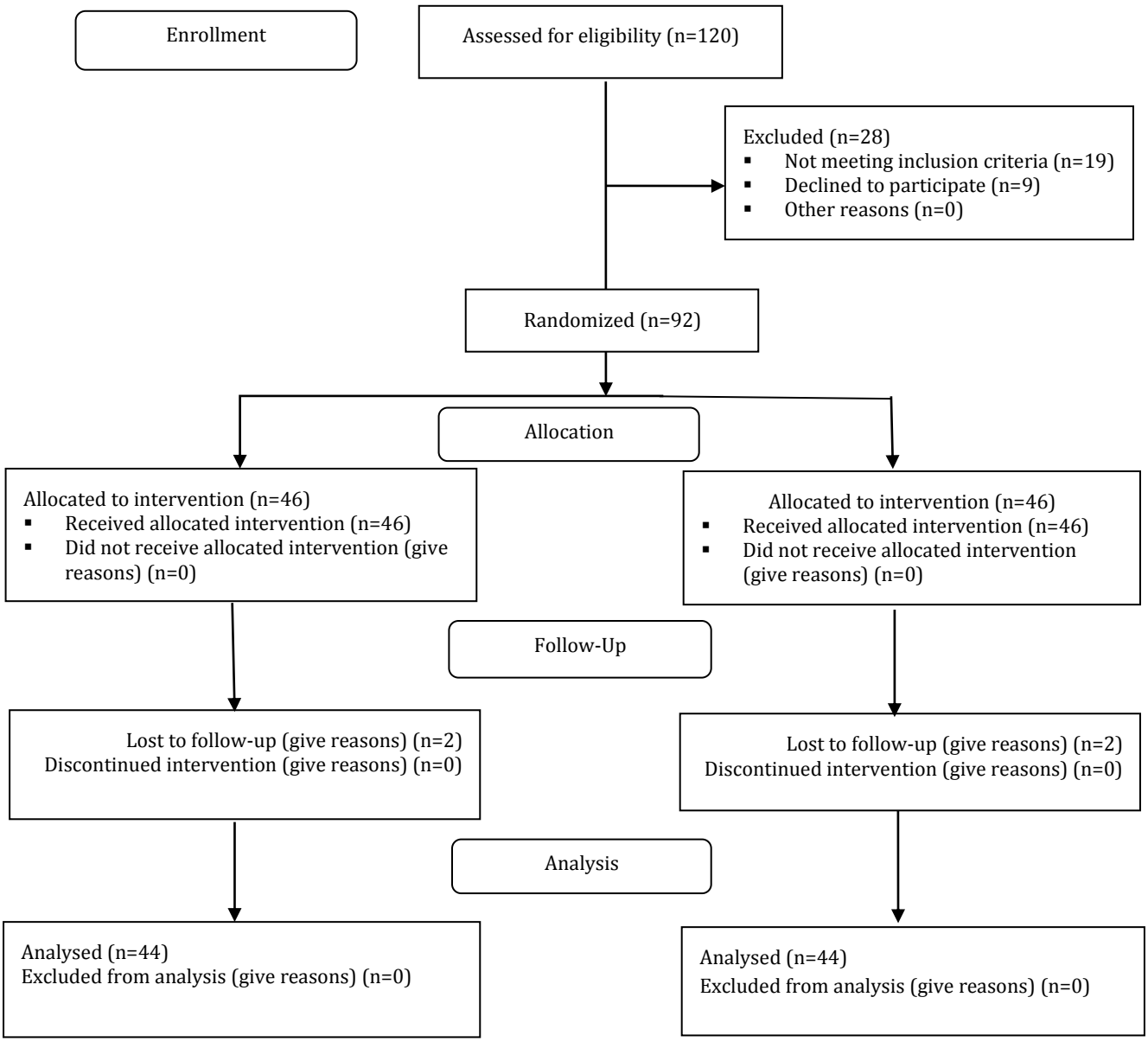

Figure 1. The CONSORT flow diagram of intervention in the two groups

Data were analyzed by SPSS software (version 22). Descriptive statistics were used to describe the demographic and clinical characteristics of the patients. The chi-square test or Fisher's exact test was used to check and compare qualitative variables between the two groups. $P< 0.05$ was considered statistically significant.

Results

About half of the participants in the tranexamic acid group were in the age range of 30 to 35 years and mostly lived in the city (72.72%). Moreover, 36.36% of the participants in the intervention group had a university education, compared to 29.54% in the cryotherapy group. Also, 22.72% of women in the intervention group and 34.09% in the control group were employees. In addition, 54.54% of the participants in the intervention group were multiparous and 36.36% had a history of abortion. The results showed that there was no statistically significant difference between the group receiving tranexamic acid vaginal effervescent tablets and cryotherapy in terms of demographic variables (Table 1).

At the end of the intervention, 97.72% and 93.18% of the participants reported improvement in clinical symptoms following tranexamic acid and cryotherapy, respectively. Although the rate of clinical improvement was higher in the group receiving tranexamic, it was not statistically significant (P =0.31) (Table 2).

Table 1. Demographic characteristics of the participants in the study

Variables	# Tranexamic acid	# Cryotherapy	P-Value
Age			
20-30 years	12(27.27)	10(22.72)	
30-35 years	21(47.73)	18(40.91)	0.51
>35 years	11(25)	16(36.36)	
Education			
Illiterate	6(13.64)	3(6.82)	
High school	10(22.72)	13(29.54)	0.56
Diploma	12(27.27)	15(34.09)	
College	16(36.36)	13(29.54)	
Residence place			
City	32(72.72)	30(68. 18)	0.64
Village	12(27.27)	14(31.82)	
Job			
Employee	10(22.72)	15(34.09)	
Household	17(38.63)	21(47.73)	0.09
Free job	17(38.63)	8(18.18)	
Parity			
Nulliparous	7(15.91)	7(15.91)	
Primiparous	13(29.54)	9(20.45)	0.58
Multiparous	24(54.54)	28(63.63)	
History of abortion			
Yes	16(36.36)	10(22.72)	0.16
No	28(63.63)	34(72.72)	

#Data are reported as numbers (percentage)

Table 2. Comparison of clinical improvement of patients in the two groups of tranexamic acid and cryotherapy at the end of the treatment period

Variable	Tranexamic acid (N=44)#	Cryotherapy (N=44)#	P-Value*
	N (%)	N (%)	
Clinical Improvement			
Yes	43(97.72)	41(93.18)	0.31
No	1(2.27)	3(6.82)	

*Fisher exact test #Data are reported as numbers (percentage)

At the end of the intervention, disease recurrence occurred in 3 patients in the group receiving tranexamic acid and one patient in the cryotherapy group. There was no statistically significant difference between the two groups in terms of disease recurrence (p =0.64) (Table 3).

At the end of the treatment period, there was no significant difference in patient satisfaction based on the Likert scale between the two groups treated with tranexamic acid effervescent vaginal tablets and cryotherapy (P=0.57). No patient was dissatisfied with the use of tranexamic acid (Table 4). No specific side effect was reported in any of the intervention and control group patients.

Table 3. Comparison of disease recurrence in the two groups of tranexamic acid and cryotherapy at the end of treatment

Variable	Tranexamic acid (N=44)	Cryotherapy (N=44)#	P-Value*
	N (%)	N (%)	
Recurrence			
Yes	3(6.82)	2(4.55)	0.64

#Data are reported as numbers (percentage)

Table 4. Comparison of patients' satisfaction with cryotherapy and tranexamic acid at the end of the third month of the intervention

Variable	Tranexamic acid (N=44)#	Cryotherapy (N=44)#	*P value
Dissatisfaction	0	2(4.54)	
Low satisfaction	0	1(2.27)	
Moderate satisfaction	7(15.91)	6(13.63)	0.57
Good satisfaction	4(9.09)	3(6.82)	
Completely satisfied	33(75)	32(72.72)	

*Fisher's exact test # Data are reported as numbers (percentage)

Discussion

The present study was conducted to compare clinical improvement, disease recurrence, and patient satisfaction following treatment with vaginal effervescent tablets of tranexamic acid and cryotherapy in patients with symptomatic cervical ectropions The results of the present study show a high rate of clinical improvement of cervical ectropion symptoms in both groups treated with vaginal tranexamic acid and cryotherapy; tranexamic acid can be as effective as cryotherapy in the clinical improvement of patients. Also, there was no significant difference in the rate of disease recurrence after tranexamic acid and cryotherapy. The level of patient satisfaction with both methods was high, and no patient was dissatisfied with the use of tranexamic acid.

Greg et al. (2020) in a clinical trial study in India showed that vaginal tranexamic acid was effective in reducing the clinical symptoms of cervical ectropions compared to betadine and had no side effects. After taking tranexamic acid, 100% of patients reported improvement in symptoms of pelvic pain and bleeding after intercourse, but the improvement of leucorrhea was 87.5% (16). Also, in the study of Anter et al (2017). 87% improvement in the signs and symptoms of cervical ectropion (including leucorrhoea, pelvic pain, contact bleeding, and improvement in the clinical appearance of ectropion) was reported after treatment with tranexamic acid (18). In the present study, disease recurrence was reported in 6.82% of women, which was not investigated in the previous two studies.

Trans-4-(Aminomethyl)cyclohexane Carboxylic Acid (T-AMCHA) is an effective factor in hemostasis and an inhibitor of plasmin and plasminogen. This drug is used orally, by injection, and locally in the treatment of bleeding and can reversibly inhibit the activity of plasminogen and subsequently inhibit fibrinolysis and reduce bleeding (20). The

results of the studies show the anti-inflammatory and anti-angiogenic effect of tranexamic acid, since the inflammatory factors increase in the cervix of women with cervicitis, it seems that Transamic performs this effect by inhibiting angiogenesis and inflammation (21). The results of a study on the cytotoxicity of topical tranexamic acid show that wound re-epithelialization using tranexamic acid does not cause cytotoxicity (22). In the present study, none of the patients experienced adverse clinical effects following the use of topical tranexamic acid.

Cervical ectropions are associated with disturbing clinical symptoms such as increased leucorrhea, dyspareunia, spotting after intercourse, pelvic pain, pain in the suprapubic region, and an increase in cervicitis and vaginitis (1, 4, 23). The fragility of the cylindrical cells and their placement in the vaginal environment makes them susceptible to contact damage, especially during sexual intercourse; so that 5-25% prevalence of spotting after intercourse has been reported in these women (24). Since in this disease, the level of cylindrical cells secreting mucus that are placed in the vaginal environment increases, leucorrhea is one of the most important complaints in these women; these discharges are mostly non-purulent and may be white or yellowish (1).

Many physicians believe that if ectropions are accompanied by clinical symptoms, they need treatment. Today, many treatments are proposed for the destruction of ectopic areas, but the cost-effectiveness of these treatments and ease of use are important issues that limit the use of these methods (25). Cryotherapy has been proposed as one of the most widely used techniques for the treatment of cervical ectopies. In this method, using very low temperatures, cell cytosols are crystallized, and eventually, cell destruction occurs. Cryosurgery was introduced in the late 1960s for the treatment of cervical intraepithelial neoplasia and has been proven to be a reliable treatment method with limited side effects (26). This method is used to treat lesions of the cervix, vagina, endometrium and vulva (26).

Various studies indicate the high effectiveness of this method in improving the clinical symptoms of patients with clinical ectropions. Mohanty et al. (1985) reported a clinical improvement rate of 98% following cryotherapy, which was 93.18% in the present study (12). In the study by Katakdhond et al. (2017) the effectiveness of cryotherapy in improving ectropions 12 weeks after cryotherapy treatment was 96%, and only one person out of 30 women participating in their study was not treated, and the patient's satisfaction with the treatment was very high (14). In the present study, 72.72% of women were very satisfied with this method. In another study conducted on 124 women with symptomatic cervical ectropion, cryotherapy was associated with 89% improvement in the symptoms of leucorrhoea and the lowest level of effectiveness was related to pelvic pain (50% improvement) (4).

The design of the pharmaceutical form of the drug in the form of vaginal effervescent tablets not only does not have the disadvantages of gel and solution forms, but also, due to the presence of effervescent elements (in the permissible limit and non-stimulating) provides the possibility of quick opening of the tablet with the lowest water content, so it has a fast onset of action, effective local action, minimal systemic side effects, and ease of use (26).

Since this study is the first study to compare the effect of tranexamic acid and cryotherapy, it has some limitations. The rate of clinical recurrence and clinical improvement of symptoms was checked by the researcher, and there was no standard tool for this measurement, which could increase the risk of bias. On the other hand, since the comparison group was treated with cryotherapy, blinding was not done completely in this study and the participants knew what type of treatment they received, which can also increase the source of bias. It is recommended that future studies be conducted with a larger sample size. Additionally, the impact of this medication on the treatment of abnormal Pap smears should also be investigated.

Conclusion

The vaginal effervescent tablets of tranexamic acid had a significant effect on improving the clinical symptoms of patients with symptomatic cervical ectropions; the rate of recurrence was low, and most of the participants were satisfied

with their use. Considering the similar effectiveness of tranexamic acid and cryotherapy in improving the clinical symptoms of patients, this method can be a suitable alternative to cryotherapy.

Acknowledgements

This article is taken from the dissertation for MD in Obstetrics and Gynecology, which was done with the financial support of Zanjan University of Medical Sciences, Zanjan, Iran. We hereby acknowledge and thank the Clinical Research Unit of Ayatollah Mousavi Hospital.

Conflicts of interest

The authors declared no conflicts of interest.

References

1. Aggarwal P, Ben Amor A. Cervical Ectropion. StatPearls Publishing, Treasure Island (FL); 2023. PMID: 32809544.
2. Wright KO, Mohammed AS, Salisu-Olatunji O, Kuyinu YA. Cervical Ectropion and Intra-Uterine Contraceptive Device (IUCD): a five-year retrospective study of family planning clients of a tertiary health institution in Lagos Nigeria. BMC Research Notes. 2014; 7(1): 1-6.
3. Soares LC, Braz FLTA, Araujo AR, Oliveira MAP. Association of sexually transmitted diseases with cervical ectopy: A systematic review. Sexually Transmitted Diseases. 2019; 46(7): 452-457.
4. López-Filloy M, Cortez FJ, Gheit T, Cruz y Cruz O, Cruz-Talonia F, Chávez-Torres M, et al. Altered Vaginal Microbiota Composition Correlates With Human Papillomavirus and Mucosal Immune Responses in Women With Symptomatic Cervical Ectopy. Frontiers in Cellular and Infection Microbiology. 2022: 12(884272): 580.
5. Pourseify GR, Mehrafza M, Raoufi A, Nikpouri Z, Askari M, Hosseinzadeh E, Razeghian K, Hosseini A. The Prevalence of High-risk Human Papillomavirus Type 16 and 18 in Women in Rasht-Iran. Journal of Midwifery & Reproductive Health. 2021; 9(3).
6. Yang K, Li J, Liu Y, Ma B, Roberts H, Tan J, et al. Microwave therapy for cervical ectropion. The Cochrane Database of Systematic Reviews. 2007; 2007(4): Cd006227.
7. Tang S, Zhou X. The cytopathologic diagnosis of cervical lesions and uterocervical carcinomas. Zhonghua fu chan ke za zhi. 1995; 30(1): 10-14.
8. Franceschi S. Past and future of prophylactic ablation of the cervical squamocolumnar junction. Ecancermedicalscience. 2015; 9(1): 527.
9. Çekmez Y, Şanlıkan F, Göçmen A, Vural A, Türkmen SB. Is Cryotherapy Friend or Foe for Symptomatic Cervical Ectopy? Medical principles and practice. international journal of the Kuwait University, Health Science Centre. 2016; 25(1): 8-11.
10. Chen J, Zhou D, Liu Y, Peng J, Li C, Chen W, et al. A comparison between ultrasound therapy and laser therapy for symptomatic cervical ectopy. Ultrasound in Medicine & Biology. 2008; 34(11): 1770-1774.
11. Aitah NF, Hamouda MS, Ahmed AY, Elsokary AA. Evaluation of autologus platelet-rich plasma versus silver nitrate in the treatment of cervical erosion. Tanta Medical Journal. 2021; 49(2): 79.
12. Mohanty K, Rand R, Berry B. Cryotherapy in the management of cervical ectopy. Sexually Transmitted Infections. 1985; 61(5): 335-337.
13. Johnston MH. Cryotherapy and other newer techniques. Gastrointestinal Endoscopy Clinics. 2003; 13(3): 491-504.
14. Katakdhond S, Samant P. Cryotherapy for cervical lesions: efficacy and patient satisfaction. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2017; 6(6): 2331–2336.
15. Patel KD, Karnavat RD, Viramgama DG, Dalal RK. Evaluation of efficacy and safety of cryotherapy in benign and premalignant cervical lesion. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2021; 10(8): 3066-3072.
16. Garg N. Clinical Study of Tranexamic Acid in Treatment of Cervical Ectopy-An Institutional Experience. Gynecology & Obstetrics. 2020; 10(1): 525.
17. Zhu J-W, Ni Y-J, Tong X-Y, Guo X, Wu X-P, Lu Z-F. Tranexamic acid inhibits angiogenesis and melanogenesis in vitro by targeting VEGF receptors. International Journal of Medical Sciences. 2020; 17(7): 903.
18. Anter SS. Clinical Effect of Tranexamic Acid on Curing Cervical Erosion. Imperial Journal of Interdisciplinary Research. 2017; 3(1): 5-9.
19. Taeuber I, Weibel S, Herrmann E, Neef V, Schlesinger T, Kranke P, et al. Association of intravenous tranexamic acid with thromboembolic events and mortality: a systematic review, meta-analysis, and meta-regression. JAMA Surgery. 2021; 156(6):

e210884-e.
20. Barrett CD, Kong YW, Yaffe MB. Influence of tranexamic acid on inflammatory signaling in trauma. Semin Thromb Hemost. 2020; 46(2): 183-188.
21. Gkiatas I, Kontokostopoulos A-P, Tsirigkakis SE, Kostas-Agnantis I, Gelalis I, Korompilias A, et al. Topical use of tranexamic acid: Are there concerns for cytotoxicity. World Journal of Orthopedics. 2022; 13(6): 555.
22. Mazur Y, Pyrohova V. Analysis of complicated cervical ectopy clinical course and recurrence. Health Sciences. 2018; 31(1): 17-26.
23. Selo-Ojeme DO, Dayoub N, Patel A, Metha M. A clinico-pathological study of postcoital bleeding. Archives of gynecology and obstetrics. 2004; 270(1): 34-36.
24. Sakhipova GZ, Abenova NA, Zhumabaeva TN, Seypenova AN, Shamshaeva DO. Clinical Experience in Management of Patients with Cervical Erosion and Ectopia. Open Access Macedonian Journal of Medical Sciences. 2020; 8(27): 226-230.
25. Buruiana FE, Gujar R, Gupta B. Minor Procedures in Gynaecological Oncology. Gynecological Oncology. 2022; 87-105.
26. Patki M, Giusto K, Gorasiya S, Reznik SE, Patel K. 17-α hydroxyprogesterone nanoemulsifying preconcentrate-loaded vaginal tablet: A novel non-invasive approach for the prevention of preterm birth. Pharmaceutics. 2019; 11(7): 335.