







Effectiveness of tranexamic acid on bleeding in conization

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ABSTRACT

Objective: Bleeding is the most common complication of conization of cervix. Hemostatic sutures, intraoperative ferric subsulfate, or vasopressin can be used when intraoperative bleeding occurred, whereas oral tranexamic acid (TA) may be used for post-operative bleeding. In this study, we aimed to find out whether intraoperative cervical TA administration in patients undergoing conization caused changes in the amount of intraoperative bleeding and post-operative hemogram.

Material and Methods: Patients who have undergone cervical conization between January 2019 and July 2019 in Zeynep Kamil Health Application and Research Center Gynecological Diseases and Birth Clinic were evaluated. One hundred and five patients were included to our study. One ampoule of 10% TA was applied cervically to 47 of these patients. Both groups were evaluated in terms of measuring the intraoperative amount of blood in the aspirator, changes in post-operative hb/hct/plt values compared to the pre-operative values, and the rate of post-operative bleeding.

Results: In our study, the amount of intraoperative hemorrhage and pre-operative hemoglobin, hematocrit, and platelet values compared to the post-operative values were found to be similar in both groups.

Conclusion: Although TA has been shown to be effective on hemorrhage in benign gynecologic operations, menorrhagia, and postpartum hemorrhages, no significant effect on hemorrhage in conization with cervical TA administration has been demonstrated.

Keywords: Cervical cytology, cervical intraepithelial neoplasia, conization, human papilloma virus, tranexamic acid



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INTRODUCTION

Cervical cancer is the most common gynecological cancer in women. According to the 2018 data of Globocan, it is the fourth most frequently diagnosed cancer worldwide.^[1] In addition to being very common worldwide, it is observed more frequently in developing countries compared to developed countries.

The approach to the management of biopsy-confirmed cervical intraepithelial neoplasia (CIN) is divided into two, according to the recommendations of the American society for colposcopy and cervical pathology: observation and treatment. The aim of treatment methods is to eliminate the entire cervical transformation zone containing the abnormal tissue. CIN 2 in adult women or CIN 3 encountered at any age should be treated by excision or ablation. Cold conization is the most commonly used excisional method. Bleeding is the most common complication of conization. Hemostasis sutures, intraoperative ferric subsulfate, or vasopressin use can be counted as a precaution for intraoperative bleeding.^[2]

Tranexamic acid (TA) is a synthetic derivative of the amino acid lysine. TA is a potent antifibrinolytic agent frequently used in elective surgical procedures. TA has been shown to be successful in the treatment of abnormal uterine bleeding and postpartum bleeding.^[3–5] It has been proven that TA reduces the amount of intraoperative and post-operative bleeding when given preoperatively in cesarean section operations performed under elective conditions.^[6]

Based on all these data, we aimed to evaluate the effect of applying TA to the cervix before conization on the amount of bleeding in this study.

MATERIAL AND METHODS

In our study, patients who underwent conization in Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital, Gynecology and Obstetrics Clinic between January 2019 and July 2019 were evaluated. Ethics committee approval dated December 19, 2018 and decision number 166 was obtained from the ethics committee of our hospital. After excluding the patients with known bleeding diathesis 105 patients (47 study, 58 control) aged 20–60 years with conization indication were included in our study. The patients were selected randomly and 47 of them were intraoperatively administered 1 ampoule of 10% TA cervically. Fifty-eight of them were included in the control group without any medical application. All patients received prophylactic antibiotics before the operation. During the operation, hemostasis sutures were routinely placed on the lateral walls of the cervix at the 3 and 9 o'clock positions. Following the cold conization with the scalpel no. 11, hemostasis was achieved with electrocoagulation, and two rolled pads were placed on all patients to be removed the next morning. In patients using TA, the injection was applied equally to the four quadrants of the cervix with a 26-gauge insulin needle. All of the operations were performed by three specific operators, and no pads or gas were used in any of the patients. The patients were evaluated considering age, obstetric history, pre-operative hemoglobin/hematocrit/platelet values, conization indications, operation times, and comorbidities. Both groups were evaluated in terms of the amount of blood in the intraoperative aspirator, the change of post-operative hemoglobin/hematocrit/platelet values compared to pre-operative values, and the rate of post-operative bleeding.

Table 1: Demographic data of patients

	Tranexamic acid (n=47) (Mean±SD, Median±Min–Max)	Control (n=58) (Mean±SD, Median±Min–Max)	p
Age (year)	44.91±9.4	42.24±9.27	0.147
BMI (kg/m ²)*	26.09±4.21	25±4.33	0.200
Gravida	3 (0–6)	3 (0–10)	0.681
Parity	2 (0–4)	2 (0–5)	0.303
Type of delivery			0.941
Vaginal	37 (78.7%)	46 (79.3%)	
C-section	10 (21.3%)	12 (20.7%)	
HPV state**			0.098
Positive	39 (83%)	41 (70.7%)	
Negative	4 (8.5%)	3 (5.2%)	
Unknown	4 (8.5%)	14 (24.1%)	

*BMI: Body mass index=Weight/Lenght²; **HPV: Human papilloma virus; SD: Standard deviation.

Data analysis was performed using SPSS for Windows (Version 20.0. 2011, IBM Corp. Armonk, NY, USA). Histograms, normality plots, and Shapiro–Wilk normality tests were used for data distribution analysis. Median, mean, standard deviation, frequency, and ratio expressions were used for descriptive statistics. Mann–Whitney U-test was used in the analysis of numerical data. Chi-square test and Fisher's exact test were used in the analysis of qualitative data. $p < 0.05$ was considered statistically significant.

RESULTS

A total of 105 patients were included in our study. While 47 of these patients were in the study group, 58 of them were in the control group.

Age, body mass index (BMI), gravida, and parity were similar in both control and study groups. When classified according to the mode of delivery, vaginal birth was calculated similar as 46 (79.3%) in the control group and 37 (78.7%) in the study group (Table 1).

In the control group, conization was performed in three patients due to persistent CIN1, 14 patients with CIN2, 33 patients with CIN3, five patients due to smear-biopsy incompatibility, and three patients due to cervical dysplasia of unknown degree. In the study group, conization was performed in one patient due to persistent CIN1, 16 patients with CIN2, 23 patients with CIN3, four patients due to smear-biopsy incompatibility, and two patients due to cervical dysplasia of unknown degree (Table 2).

In the control group, three patients had asthma, one patient had arrhythmia, one patient had diabetes, three patients had hypothyroidism, two patients had hypertension, and two patients had both diabetes and hypertension. In the study group, one patient had asthma, one patient had diabetes, one patient had hypothy-

Table 2: Pre-operative smear results, indications, and endocervical curettage results after conization

	Tranexamic acid (n=47) (Mean±SD, Med±Min–Max)	Control (n=58) (Mean±SD, Med±Min–Max)	p
Smear			0.806
Insufficient	2 (4.3)	3 (5.2)	
Normal	20 (42.6)	21 (36.2)	
ASCUS	8 (17)	7 (12.1)	
ASC-H	3 (6.4)	5 (8.6)	
LSIL	8 (17)	9 (15.5)	
HSIL	6 (12.8)	13 (22.4)	
Indications			0.754
Persistent CIN 1	1 (2.1)	3 (5.2)	
CIN 2	16 (34)	14 (24.1)	
CIN 3	23 (48.9)	33 (56.9)	
Smear-biopsi mismatch	4 (8.5)	5 (8.6)	
Others	3 (6.4)	3 (5.2)	
Endocervical curettage			0.649
Normal	30 (63.8)	39 (67.2)	
CIN 1	2 (4.3)	3 (5.2)	
CIN 2	6 (12.8)	9 (15.5)	
CIN 3	9 (19.1)	7 (12.1)	

ASCUS: Atypical squamous cells of undetermined significance; ASC-H: Atypical Squamous cells-cannot exclude high-grade squamous intraepithelial lesion; LSIL: Low grade intraepithelial lesion; HSIL: High grade intraepithelial lesion; SD: Standard deviation; Med: Median; CIN: Cervical intraepithelial neoplasia.

roidism, four patients had hypertension, one patient had hypertension and diabetes, one patient had hypertension and hyperthyroidism, and one patient had hypertension and hypothyroidism.

In our study, the mean amount of bleeding was 103.9 ± 71.4 in the control group, while it was 87.55 ± 86.36 in the study group. However, when these two values were compared, p value was calculated as 0.291, so no significant difference was observed. When both groups were evaluated in terms of changes in hemoglobin and hematocrit values, it was calculated as $1.48 \pm 0.64/4.12 \pm 2.04$ in the control group, and $1.56 \pm 0.76/4.49 \pm 2.10$ in the study group. In other words, when the intraoperative bleeding amounts and post-operative hemoglobin, hematocrit, and platelet values of both groups were evaluated according to their preoperative values, the results were similar (Table 3).

After conization, bleeding that required early intervention did not occur in either groups, and no blood transfusion was required due to bleeding.

DISCUSSION

Cervical cancer ranks fourth among the most frequently diagnosed cancers in the world.^[1] Cervical cancer screenings have increased the diagnosis of CIN and the use of treatment methods along with it. Cold conization is the oldest method used in the treatment of CIN and in the exclusion of cervical cancer.

Bleeding is the most common complication of conization. It can be observed intraoperatively or postoperatively. Bleeding is inevitable during conization, but it can usually be controlled with conservative techniques such as suturing and cauterization. Bleeding is also important in terms of impairing the vision of the operation area. Hemostasis sutures, intraoperative ferric subsulfate, or vasopressin can be used as a precaution.^[2] Rarely, in cases where bleeding cannot be controlled, internal iliac artery embolization or ligation or hysterectomy may be required. In a case report by Giannella et al.,^[7] it is mentioned that an active bleeding that occurs during LEEP application and cannot be controlled by suturing the cervix is to control bleeding with a cervix maturing balloon. Post-operative bleeding is seen between 5 and 15% and is often associated with inadequate intraoperative hemostasis.^[8–10]

In this study, we evaluated the amount of intraoperative bleeding and the change in post-operative hemograms by applying intraoperative cervical TA to patients who underwent conization.

In a study comparing three techniques, cold conization, electric knife conization, and LEEP, the results of residual disease, post-operative bleeding, cervical stenosis, and recurrence were compared.^[11] While the volume of the removed biopsy material was higher in cold conization and electric knife conization ($18.3–4.7/18.4–0.7$ mm) compared to LEEP materials ($12.8–3.5$ mm), there was no significant difference in recurrence rates. While the cold conization was evaluated with 8% the highest in post-operative bleeding rates, it was seen as 5% in electric knife conization and 2% in LEEP. In another study by Saidi et al.,^[12] cold conization and LEEP were compared and the amount of intraoperative bleeding was found to be significantly less in patients who underwent LEEP. For this reason, we did not include patients who underwent LEEP and reconization in our study. The volume of the extracted material ($3.32–3.14$ mL) was also evaluated as similar between the control and study groups.

Scott et al.^[13] evaluated the post-operative bleeding rates by performing cold conization after injecting diluted adrenaline solution into the cervical stroma. Minor post-operative bleeding was observed in 9.7% of 88 patients, while post-operative infection was observed in 2.9%. These rates were found to be compatible with the literature. Between January 2019 and July 2019, a total of 164 leep, conization, and reconization cases were performed in our clinic. Leep and reconizations were eliminated and 105 of these cases were included in our study. Contrary to the rates in the literature, no post-operative bleeding requiring intervention was observed in any of the patients who underwent these operations in our clinic. Furthermore, post-operative infection was not observed in any of the patients. The fact that our hospital is one of the few reference hospitals in the field of gynecological oncology with a colposcopy center in Istanbul and its conization experience is quite high explains this situation.

Table 3: Perioperative values of the patients

	Tranexamic acid (n=47)	Control (n=58)	p
	Mean±SD	Mean±SD	
Pre-operative hemoglobin (g/dL)	13.15±1.25	12.79±1.20	0.136
Pre-operative hematocrit (%)	39.47±3.25	38.64±3.18	0.186
Pre-operative thrombocyte (/mm ³)	278 500±72 075	281 000±70 700	0.820
Operation time (min)	32.45±6.07	31.47±5.13	0.371
Material volume (mL)	3.14±1.5	3.32±1.24	0.486
Hemoglobin change	1.56±0.76	1.48±0.64	0.529
Hematocrit change	4.49±2.10	4.12±2.04	0.362
Amount of bleeding (mL)	87.55±86.36	103.9±71.4	0.291
Post-operative hemoglobin (g/dL)	11.61±1.2	11.31±1.2	0.208
Post-operative hematocrit (%)	35.06±3.02	34.52±3.17	0.376
Post-operative thrombocyte (/mm ³)	233 360±57 170	240 000±56 850	0.562
Length of hospital stay (h)	22.81±6.24	23.45±2.95	0.490

SD: Standard deviation.

TA was evaluated for its effect on blood loss after conization in a double-blind randomized study by Rybo et al.,^[14] 50 patients who applied to their clinics with dysplasia or non-invasive cervical cancer were included in this study, and five of them were excluded from the study for various reasons. Oral TA was administered to these patients in the form of three tablets (4.5 g per day) at 8-h intervals for 12 days, starting on the evening of the operation. In terms of bleeding, the patients were followed in the hospital for the 1st 7 days, and blood loss was observed to be reduced in the TA group compared to the placebo group (23±3.2/79±20.4 mL). Post-operative sudden bleeding was observed only in 7 patients in the placebo group. On the other hand, we used 1 ampoule of TA (250 mg) cervically just before the operation to apply once in our study. When the effectiveness of cervical TA on intraoperative and early bleeding was compared, the amount of intraoperative bleeding was 87.55±86.36 in the study group and 103.9±71.4 in the control group. p value was calculated as 0.291. No significant difference was observed between these two groups. New studies can be planned with different application methods and increasing doses.

In a review of 12 randomized controlled trials, including this study by Rybo et al.,^[14] 1512 of 1602 women in total could be followed up to the end of the study. In this review, vasopressin, TA, and vaginal packing were evaluated in terms of their effectiveness in bleeding due to conization. Compared with placebo, TA was found to significantly reduce bleeding (risk ratio [RR]=0.23, 95% confidence interval [CI] 0.11–0.50) in cold conization and laser conization. Contrary to this situation, its effectiveness could not be demonstrated in the primary hemorrhages (RR=1.24, 95% CI 0.04–38.23). In this review, which was updated in 2013, TA was found to significantly reduce post-operative blood loss when compared to placebo.^[15] In all these studies, TA was used in intraoperative intravenous and post-operative oral form for 12–14 days.

Although vaginal bleeding is frequently seen in advanced cervical cancers, it can be life-threatening. Bleeding is the cause of sudden death in 6% of women with cervical cancer.^[16] In the Cochrane review, which Eleje et al.^[16] updated in 2019, randomized and non-randomized comparative studies between 2015 and 2018 were evaluated. In these studies, the safety and effectiveness of TA, vaginal packing, and interventional radiology compared to radiotherapy in the palliative treatment of vaginal bleeding in women with advanced cervical cancer were investigated. However, this review did not find sufficient evidence to show the superiority of one method over the other. More randomized controlled studies have been suggested in this area.

In a recent placebo-controlled randomized clinical study, TA was used prophylactically in elective cesarean sections and it was found that it reduced mean blood loss by 25.3%. It was observed that bleeding and transfusion requirement of 1000 mL and above decreased significantly in the TA group.^[17]

In our study, the mean amount of bleeding was 103.9±71.4 in the control group, while it was 87.55±86.36 in the study group. However, when these two values were compared, p value was calculated as 0.291, so no significant difference was observed. However, since our hospital is a reference hospital, the operator experience is quite high. We think that intraoperative TA administration will yield more efficient results in clinics with less operator experience. When both groups were evaluated in terms of changes in hemoglobin and hematocrit values, it was calculated as 1.48±0.64/4.12±2.04 in the control group, and 1.56±0.76/4.49±2.10 in the study group.

Our work was carried out by three specific operators to reduce operator dependency. Technically, the same method was applied in all cases and the LEEP and reconization patients were not included in the study, thus eliminating the difference in the amount of bleeding due to the technique and increased the reliability of the study. The volume of material removed in both groups was evaluated as similar.

CONCLUSION

Although TA has been shown to be effective on bleeding in benign gynecological operations, menorrhagia, and postpartum hemorrhages, it has not been shown to have a significant effect on bleeding in conizations with cervical application. To evaluate the effectiveness of TA on bleeding in patients undergoing conization, new studies can be conducted in larger patient groups and with different application methods.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 19.12.2018, number: 166).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ABAD, BG; Design – BG, CKK; Supervision – CKK, EBE; Resource – ABAD; Materials – ABAD; Data Collection and/or Processing – ABAD, PÖ, ÖA; Analysis and/or Interpretation – ABAD, EBE; Literature Search – ABAD; Writing – ABAD, EBE; Critical Reviews – EBE.

Conflict of Interest: The authors have no conflict of interest to declare.

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