Original Article

Use of Tranexamic Acid in Bleeding Control of Transabdominal and Transvaginal Hysterectomy

Abstract

Background: Hysterectomy is one of the most common gynecology surgeries. This study aimed to compare perioperative bleeding in transabdominal and transvaginal hysterectomy. **Materials and Methods:** This prospective, double-blind, randomized, controlled clinical trial was performed on 80 patients undergoing hysterectomy referred to Shahid Beheshti Hospital, Isfahan, Iran. Patients were divided into two groups of 40; the first group (T) received 1 g intravenous tranexamic acid (TXA) for 20 min preoperatively. The second group (S) received 10 cc normal saline as placebo. Blood samples were taken before and 12 h after surgery for assessment of hemoglobin, hematocrit, and platelet count, the prothrombin time, activated partial thromboplastin time, and serum creatinine as well as volume of blood transfusion. **Results:** There were no significant differences between the two groups in heart rate, diastolic blood pressure (BP), systolic BP, and mean arterial pressure before, during, and after surgery ($P > 0.05$). There was no significant difference in blood variables before and after surgery ($P > 0.05$) except the platelet count that was in the normal range in both groups after surgery ($P = 0.022$). The mean volume of blood transfused in the case group was significantly lower than the control group during surgery ($P = 0.008$) and 12 h after surgery ($P = 0.01$). **Conclusion:** The prophylactic administration of TXA results in a significant reduction in need for blood transfusion and the duration of surgery. Given the lower risks of using TXA compared to the other drugs, it is recommended in hysterectomy to control bleeding.

Keywords: *Bleeding, hysterectomy, Tranexamic Acid*

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Introduction

Major gynecologic surgeries, including hysterectomy, are associated with excessive perioperative blood loss and women may require a blood transfusion before surgery. Surgery can potentially affect the coagulation system and the fibrinolytic system is suppressed due to the release of fibrinogen activator inhibitor.[1,2] Blood transfusion is associated with increased complications and morbidity; both surgical procedures with more precise and antifibrinolytics are required to improve hemostasis to reduce the amount of bleeding during major gynecologic surgery.[3] Current antifibrinolytic agents, such as aprotinin, which inherently inhibit serine protease, are synthetic inhibitors of nafamostat proteases, and synthetic lysine analogs of aminocaproic acid and tranexamic acid (TXA).[4,5] Synthetic lysine analogs bind reversibly to the lysine binding sites on plasminogen and prevent the conversion of plasminogen to plasmin on the fibrin surface. TXA is a competitive inhibitor of plasminogen activation. The intravenous TXA has been shown to be very useful in reducing blood loss and need for blood transfusion during coronary artery bypass,[6] spinal surgery,[7] maxillofacial surgery,[8] and total hip or knee arthroplasty.[9] Abnormal uterine bleeding (AUB) is one of the most common reasons for referral to gynecology clinics, accounting for 20% of cases. TXA effectively reduces the AUB.[10] This drug has been used successfully to reduce excessive blood loss in gynecologic surgeries during myomectomy[11] and postpartum hemorrhage.[11] Therefore, the aim of this study was to compare perioperative bleeding in transabdominal and transvaginal hysterectomy.

Materials and Methods

A prospective, double-blind, randomized, controlled clinical trial was performed on 80 patients undergoing hysterectomy who were referred to educational hospitals affiliated to Shahid Beheshti University

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of Medical Sciences, Isfahan, Iran. Considering the 99% confidence level, 99% test power, and bleeding rate from previous studies[12] in the two groups receiving TXA and the control group (mean ± standard deviation), respectively, equal to 84.3 ± 16.64 and 106.16 ± 22.96, the sample size was estimated as 40 people in each group. Patients were randomized to two groups, each comprising 40 patients according to a two-blocked randomization list which was coded (1 or 2) at a 1:1 ratio. The two parallel groups were prepared using a computer-generated randomization system. Inclusion criteria included patients aged 35–70, indication of transabdominal and transvaginal hysterectomy, and American Society of Anesthesiologists Physical Status I–II patients. Having a TXA allergy and dissatisfaction with participation were considered as non-inclusion criteria and if the patients were not willing to continue the study they were excluded.

The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences with the code of IR.MUI.MED.REC.1369.3.201. All the necessary information about the surgical procedure and the administration method of TXA as well as the purpose of the study was provided to the patients. The informed consent form was signed by each participant. Patients were divided into two groups, each with 40 patients using the random allocation software [Figure 1]. The first group (Group T) received 1 g of intravenous TXA for 20 min before performing a surgical procedure and making the first surgical incision. The second group (Group S) received 10 cc of normal saline placebo. Both nurse, who administered the medication, and the patient were not aware of the type of drug used. TXA 1 g (10 cc) was diluted in glucose 5% (20 cc). After the patient entered the operating room, routine monitors (such as noninvasive blood pressure [BP] monitor, electrocardiogram (ECG), and pulse oximeter) were performed and infusion of isotonic crystalloids (normal saline) was done. The patient received either general or spinal anesthesia in a similar manner. Arterial BP, heart rate (HR), and ECG were continuously measured during the surgery. Despite adequate fluid administration, if the patient had symptoms of hemodynamic instability due to bleeding (an HR of more than 100 beats/min or systolic BP >20% of baseline), blood transfusion was started. Blood loss in milliliters during the surgery was assessed by the amount of blood gases and the estimation of the volume of blood in the suction tank and after the operation and during the recovery by controlling the patient's drains. Blood samples were taken from all patients before and 12 h after surgery for hemoglobin, hematocrit, and platelet count, the prothrombin time (PT), activated partial thromboplastin time (PTT), and serum creatinine. In addition, the volume of blood transfusion was recorded in all patients during and 12 h after surgery. Moreover, the patients' demographic characteristics including age, underlying disease, a history of uterine surgery, type of surgical procedure (minor/general), and underlying cause of uterine surgery were recorded in the checklist. Statistical analysis was performed using SPSS (version 20; SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean and percentage. Independent *t*-test, Chi-square, and the general linear model were used to analyze the data [Table 1].

Results

A total of 80 patients who underwent abdominal or vaginal hysterectomy were included in the study. The participants were divided equally into a case group (Group T) and a control group (Group S) (n = 40 per group). The mean age of patients in Group T was 6.5 ± 50.2 years (range 36–63) and it was 5.5 ± 48.7 years (range 38–56) for patients in Group S (P = 0.45).

The results of the present study showed that there were no significant differences between the two groups with respect to HR, diastolic BP, systolic BP, and mean arterial pressure before, during, and after surgery (P > 0.05). As shown in Table 2, no significant difference was found between the

Table 1: Frequency distribution of underlying disease, a history of prior uterine surgery, types of hysterectomy, cause of hysterectomy, and American Society of Anesthesiologists in two groups

Variable	Case group (%)	Control group (%)	*P*
Previous medical history			
No	22 (55)	32 (80)	0.23
Liver diseases	4 (10)	4 (10)	
Renal diseases	2 (5)	0	
Severe heart diseases	6 (15)	0	
Congenital or acquired coagulation disease	4 (10)	2 (5)	
History of thromboembolic disease	2 (5)	2 (5)	
History of previous surgery on uterus			
No	16 (40)	14 (35)	0.74
Yes	24 (60)	26 (65)	
Type of hysterectomy			
Minor	10 (25)	14 (35)	0.49
Major	30 (75)	26 (65)	
Cause of hysterectomy			
AUB	24 (60)	22 (55)	0.74
Endometriosis	2 (5)	2 (5)	
Cancer	6 (15)	2 (5)	
Ovarian mass	4 (10)	8 (20)	
Myoma	4 (10)	6 (15)	
ASA rate			
I	26 (65)	22 (55)	0.60
II	14 (35)	18 (45)	
Duration of surgery	154.7±34.1	161.3±32.7	0.54
Duration of stay in recovery	62.5±16.7	77.1±23.3	0.03

ASA: American Society of Anesthesiologists, AUB: Abnormal uterine bleeding

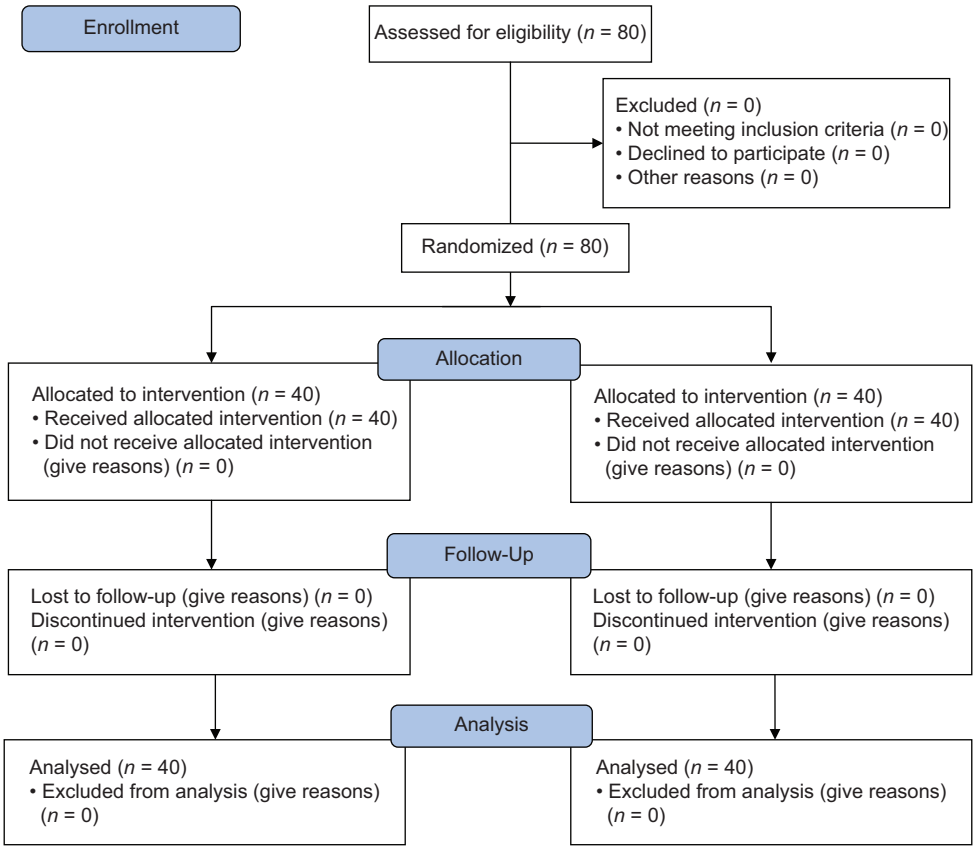

Figure 1: CONSORT flowchart

Table 2: Mean hematologic variables in the two groups before and after surgery

Variable	Case group	Control group	*P*
Preoperation			
Hemoglobin levels	12±1.5	12.1±1.6	0.91
Hematocrit level	36.76±3.7	36.77±4.04	0.99
Platelet count	25.97±3.51	25.83±6.49	0.93
Level PTT	11.2±1.02	11.9±1.4	0.12
PT level	25.4±3.1	26.8±4.4	0.24
Level INR	1.10±0.1	1.13±0.2	0.58
Postoperation			
Hemoglobin levels	11.8±1.4	11.3±1.3	0.22
Hematocrit level	35.5±4.2	34.1±3.7	0.28
Platelet count	26.51±9.17	22.04±7.86	0.022
Level PTT	11.2±1.03	11.5±1.5	0.14
PT level	25.7±4.01	26.1±3.5	0.77
Level INR	1.13±0.1	1.11±0.2	0.76

PT: Prothrombin time, INR: International normalized ratio, PTT: Partial thromboplastin time

two groups in terms of blood variables before and after surgery ($P > 0.05$) except that the platelet count was in the normal range in both groups after surgery ($P = 0.022$).

In addition, the mean amount of blood transfused to patients during surgery ($P = 0.008$) and 12 h after surgery ($P = 0.01$) in the case group was significantly lower than the control group [Table 3].

Discussion

Homeostasis depends on a balance between the coagulation/fibrinolysis cascades and the complement system. It also requires alignment among platelets, plasma proteins, blood viscosity, and endothelial structure. Damage to the walls of arteries and veins causes the cells expressing tissue factors and perivascular cells to be exposed to blood.[13] Bleeding during and after surgery can increase the hospital length of stay, the need for multiple blood transfusions, and reoperation. In addition, the increased need for blood transfusions can lead to increased risk of hemolytic reactions, anaphylaxis, acute lung injury (or acute respiratory distress syndrome), and bacterial and viral infections. On the other hand, the use of blood transfusions which can cost a lot may be associated with a shortage of available donated blood.[14] Both theoretically and practically, it has been proven that reducing bleeding during surgery, regardless of the need for reducing blood transfusion, can help improve overall vision in the surgical field and reduce the duration of surgery.[15] Antifibrinolytic agents, including TXA, epsilon aminocaproic acid (EACA), and aprotinin, are widely used to reduce bleeding in various surgeries.[14] However, aprotinin has significant side effects, including anaphylaxis, obstructive uropathy, glomerular capillary thrombi, rhabdomyolysis, and myoglobinuria, which can limit its use.[4] Therefore, it is important to evaluate the effectiveness of antifibrinolytic drugs, such

Table 3: The mean volume of blood transfused in the two groups and during surgery and 12 h after surgery

Volume of blood transfused	Case group	Control group	*P*
During the surgery	24.25±51.1	42.5±41.1	0.008
12 h after surgery	10±10	85.01±32.3	0.01
Duration of surgery	154.7±34.1	161.3±32.7	0.54
Duration of stay in recovery	62.5±16.7	77.1±23.3	0.03

as TXA, which can reduce bleeding loss during surgery. In the present study, the effectiveness of prophylactic use of TXA to reduce blood loss and transfusion in patients undergoing hysterectomy during and after surgery was investigated. No significant difference was found between the two groups in terms of confounding variables that might affect the need for blood transfusion. The patients' demographic characteristics including underlying disease, a history of uterine surgery, type of surgical procedure (minor/general), and underlying cause of uterine surgery were assessed. On the other hand, there was no significant difference between the two groups with respect to platelet count, PT and PTT, hemoglobin and hematocrit. However, a significant difference was found between the two groups in terms of platelet count after surgery, which could lead to no differences between the two groups in terms of bleeding and the need for blood transfusion because the platelet count was in the normal range in both groups. Therefore, the confounding variables that might affect the final outcomes of the two groups were identical. Our results demonstrated that the prophylactic administration of intravenous TXA significantly reduced the need for blood transfusion. Furthermore, Group T had a significantly shorter length of recovery stay, but no difference was found between the two groups in terms of the duration of surgery. In a study performed by Celebi *et al*., the administration of TXA has effectively reduced the blood loss and transfusion needs in gynecological surgeries. Furthermore, the administration of TXA significantly reduced blood loss in study group during surgery as compared to in the group treated with crystalloids and colloids. More importantly, TXA was associated with a significant reduction in the need for blood transfusion compared to EACA.[16] Contrary to our study, Lemay *et al*. showed that TXA can reduce the need for allogeneic red blood cell transfusions in patients undergoing total hip replacement.[17] In their study, Wu *et al*. examined the feasibility of a real "blood transfusion"-free hepatectomy in a large group of patients with liver tumors, and TXA 500 mg was intravenously administered just before operation followed by 250 mg, every 6 h, for 3 days. The results indicated that perioperative parenteral use of TXA reduced the amount of operative blood loss and the need for blood transfusion in elective liver tumor resection.[18] A study performed by Shakur *et al*. revealed that TXA could reduce mortality due to bleeding in women with postpartum hemorrhage with no adverse effects.[19] The results of a recent study show that preoperative intravenous TXA reduces the total blood loss irrespective of the route of hysterectomy and the number of perioperative transfusions.[20] In another study, it has been concluded that intravenous and topical TXA application is a safe and reliable method to help decrease blood loss during and after abdominal hysterectomy.[12] In our study, no incidences of serious adverse events occurred. Thus, TXA should be considered as a prophylactic treatment before benign hysterectomy.

Conclusion

The present study confirmed the findings of previous studies and the prophylactic administration of TXA yielded a significant reduction in need for blood transfusion and the duration of surgery. Given the lower risks of using TXA compared to aprotinin and its better outcomes compared to the other drugs, it is recommended that this drug can be used to prevent bleeding during and after the hysterectomy.

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Conflicts of interest

There are no conflicts of interest.

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