Short Communication

Evaluating the effectiveness of tranexamic acid administration in reducing bleeding in benign prostate hyperplasia patients underwent open prostatectomy: A double-blind randomized clinical trial

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Background: Blood loss of postoperative after prostate surgery could be related with an increase in urinary fibrinolytic activity. Tranexamic acid (TXA) is both a potent inhibitor of plasminogen and urokinase activators and a low molecular weight substance that is excreted unchanged in the urinary tract and can be administered both orally and intravenously. This study aimed to evaluate the effectiveness TXA administration in reducing bleeding in benign prostatic hyperplasia (BPH) patients who underwent open prostatectomy. **Materials and Methods:** This double-blind randomized clinical trial was conducted on patients with BPH who underwent open prostatectomy. The first group received TXA (1 gr IV from during surgery to 48 h after surgery, 3 times/day). Twenty-four hours after surgery, the two groups were compared in terms of bleeding rate. Hemoglobin (Hb), hematocrit (HCT), and platelet (Plt) counts were also assessed before and after the intervention. **Results:** Intervention and control groups were comparable in terms of basic and baseline values of variables at the beginning of the study ($P > 0.05$). The mean bleeding volume in TXA group was significantly lower than the control group 112.11 ± 53.5 and 190.00 ± 97.5 CC; $P \leq 0.001$). Mean hospitalization (3.28±0.46 vs. 4.38 ± 0.95 days $P < 0.001$) and surgery duration (98.11 ± 37.11 vs. 128.00 ± 39.12 h; $P = 0.001$) were significantly lower in TXA group compared to control intervention. **Conclusion:** According to the findings of the current study, the administration of TXA led to reduce bleeding in BPH patients who underwent open prostatectomy. Furthermore, the mean Hb, HCT, levels were significantly affected by TXA. TXA treatment approach also can reduce the surgery and hospitalization time effectively. TXA approach is recommended as effective procedure in BPH patients who underwent open prostatectomy.

Key words: Benign prostate disease, bleeding, open prostatectomy, tranexamic acid

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INTRODUCTION

Benign prostatic hyperplasia (BPH) refers to the nonmalignant growth of the prostate.[1-5] It develops as an age-related occurrence in approximately all men, starting at nearly 40-year-old. This condition can be in asymptomatic, symptomatic or microscopic, and macroscopic status.[6] The molecular etiology of BPH is unknown, although various risk factors including inflammation, genetic, age, hormones, growth factors, and lifestyle factors were identified for the development of BPH.[7] These patients show lower urinary tract symptoms, including stop-start urination, nocturia, a sensation of not completely emptying the bladder, weak

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urinary stream, straining to urinate, and a need to urinate soon after voiding.[6]

The selection of various methods for the treatment of patients with BPH is according to the severity of symptoms, size of the prostate, and other factors.[8] Open prostatectomy is one of the intervention methods in BPH therapy. One of the most important complications of open prostatectomy is bleeding. Other factors may play a role in causing bleeding and blood volume loss, including prostate weight, duration of surgery, use of acetylsalicylic acid, type of anesthesia, and age of patients.[8] In addition, bleeding can lead to hemorrhagic shock and also affect the patient's prognosis.

Various approaches including catheter traction, intravenous administration of estrogens, fibrin adhesive, phenol solution, and intraprostatic vasopressin have been used to reduce the perioperative and postoperative bleeding. Although these methods have shown some promising findings, no one approach has gained wide acceptance and incorporation into a surgical method.[8]

Perioperative antifibrinolytic therapy is considered part of the strategy of comprehensive perioperative blood management.[9] Antifibrinolytic agents such as tranexamic acid (TXA) are effective in preventing bleeding complications and decreasing mortality with minimal adverse effects.[10] TXA is a synthetic derivative of lysine and illustrates anticoagulant effects by blocking the lysine binding sites on plasminogen molecules, inhibiting the interaction of plasminogen and fibrin.[11]

The potency of TXA regarding binding affinity to plasminogen and plasmin is 6–10 times higher than similar compounds, including ε-aminocaproic acid.[12,13] TXA suppresses fibrinolysis, which is manifested as a decrease in serum D-dimer levels but does not influence serum markers of coagulopathy.[13]

Recently, a growing body of evidence has indicated that TXA is an effective agent for reducing blood loss in cardiac, orthopedic, and hepatic surgery, gynecological, transplant surgeries, and urological fields.[10] Others reported that the effect of TXA is dose-dependent and that the use of high-dose TXA is safe and effective in decreasing hemorrhage in such fields. On the other hand, due to the high incidence of BPH in our country,[12] cheaper TXA than other hemostatic drugs, lack of reports regarding TXA mortality, failure to control bleeding with other hemostatic drugs, and no comprehensive study regarding the effect of TXA in reducing bleeding in BPH patients who underwent open underwent prostatectomy in our country, this study aimed to assess the effectiveness of TXA prescription in reducing bleeding as primary outcomes in benign prostate disease patients who underwent open prostatectomy.

METHODS

Study design and participant

This double-blind randomized clinical trial was conducted on patients with BPH who underwent open prostatectomy in the Urology Department of Isfahan University of Medical Sciences in AL Zahra and Khurshid Hospitals during 2020–2021.

Inclusion and exclusion criteria

Inclusion criteria were patients with BPH aged more than 18 years who underwent prostatectomy. History of thrombotic events, bleeding disorders, chronic kidney disease (serum creatinine >180 μmol/l), and taking of anticoagulants such as aspirin and dipyridamole, high prothrombin time, and partial thromboplastin time caused patients excluded from the study.

Procedure

In the current study, 110 patients were selected and were divided into two groups (n = 55). These patients were randomly according to double-blind randomized divided into two groups. The first group received TXA (1 gr IV from starting surgery to 48 h after surgery, 3 times/day), and the second group received a placebo along with routine care. The sample size in the current study was determined by considering type-1 error (α) rate at 0.05 and power at 95% for detecting at least mean difference (63.9 ± 5.2 vs. 77.4 ± 5.0) g/dL in TXA compared to the control group for during operative bleeding from previous studies.[14] The included patients were randomly allocated into two equal groups using the closed envelope method for masking the interventions to the patients and investigator [Figure 1]. Among included patients, finally, 52 and 50 patients in TXA and control groups completed the study protocol. Figure 1 shows the CONSORT flow diagram of recruitment of patient. The reason for this decrease in the number of patients is the longer hospital stay for reasons other than those mentioned above or the occurrence of other surgical complications affecting the variables examined.

Twenty-four hours after surgery, in both TXA and control groups bleeding volume as primary outcome, hemoglobin (Hb), hematocrit, and platelet (Plt) counts before and after the intervention as well as duration of surgery, hospitalization duration as secondary outcomes were also assessed. Other data such as the age of patients and size of prostate were also recorded.

Blood loss was assessed according to the Eq. (1)

$$ABL = (EBV \times [Hi - Hf])/Hav \quad (1)$$

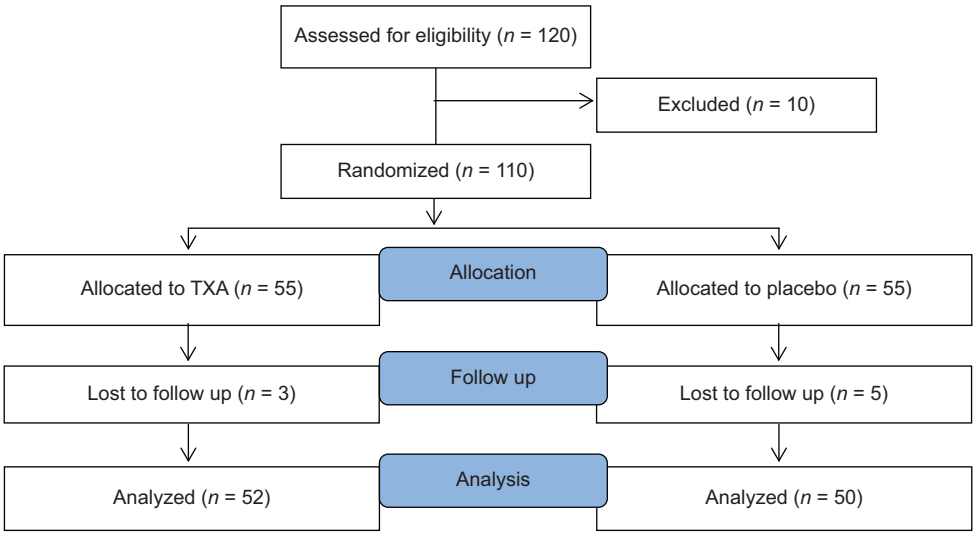

Figure 1: Consort flow diagram of patients

Hi: Initial hemoglobin

Hf: Final hemoglobin

Hv: The mean initial and final hemoglobin

EBV: body weight (kg) × average blood volume (ml/kg).

Ethical consideration

The current study was approved by the Ethics Committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1400.374). The registration reference is IRCT20211121053127N1.

Statistical analysis

Data were entered SPSS, version 21 (IBM Corp., Armonk, N. Y., USA). Continuous and categorical data were reported as mean ± Standard Deviation and frequency (percentage). The normality of continuous data was evaluated using Kolmogorov–Smirnov test and Q-Q plot. Nonnormally positive skewed data were subjected to logarithmic transformation. Paired samples *t*-test was used for comparing mean values of continuous outcomes before and after intervention and analysis of covariance was used for doing between-group comparisons in terms of mean values of study outcomes after intervention when adjustment was made for their baseline values. Chi-squared was used for comparing categorical data between two groups. Independent samples *t*-test or nonparametric Mann–Whitney *U* or Kruska–Wallis tests also was used for comparing continuous variables between groups. Spearman rank correlation coefficient was used for evaluating the correlation between bleeding volume with age, surgery, and size of prostate. $P < 0.05$ was considered as statistically significant level.

RESULTS

A total of 120 patients with urinary symptoms because of BPH were assessed for eligibility in the current study. A total of 110 patients who had inclusion criteria and agreed to participate were included in the study. Among included patients finally 52 and 50 patients in TXA and control groups completed the study protocol. Figure 1 shows the CONSORT flow diagram of recruitment of patient.

Table 1 shows the basic characteristics and baseline values of study outcomes in patients in two study groups. As can be seen, the two groups are comparable and did not any statistically significant difference (All $P > 0.05$).

The mean bleeding volume as the primary outcome in the current study in TXA group was significantly lower than the control group (112.11 ± 53.5 and 190.00 ± 97.5 CC; $P \leq 0.001$) [Figure 2]

Table 2 shows within and between groups comparison of secondary study outcomes, i.e. Hb, hematocrit (HCT), Plt. The mean values of all variables reduced significantly after intervention in both groups (All $P < 0.001$), however, the mean values of Hb ($P < 0.001$) and HCT ($P = 0.006$) showed a significantly higher reduction in the control group compared to TXA group and mean value of Plt although was lower in the control group at the 24 h after intervention however it was not statistically different from TXA group ($P = 0.145$). The mean hospitalization ($P < 0.001$) and surgery time ($P = 0.001$) were significantly lower in TXA group than the control group.

We evaluated the correlation between the bleeding volume with age, size of prostate, and surgery duration in both groups. Significant positive correlation was observed between bleeding volume with size of prostate ($r = 0.687$,

Table 1: Basic demographic and clinical characteristics of study participants in tow study groups

Variables	TXA group	Control group	*P**
Age	72.98±10.38	73.96±10.13	0.63
Tumor size	87.88±40.97	88.86±32.25	0.89
Hb	13.38±1.76	13.5±1.80	0.74
HCT	40.01±5.34	39.8±5.65	0.86
Plt	191384.6±58638	192940±57551	0.89
Anesthesia type (%)			
General	6 (11.5)	7 (14)	0.71
Spinal	46 (88.5)	43 (86)	

*Resulted from independent samples *t*-test or Chi-squared test for continuous or categorical data. Hb=Hemoglobin, HCT=Hematocrit, Plt=Platelet, TXA=Tranexamic acid

Table 2: Within and between groups comparisons of secondary outcomes in tranexamic acid and control groups

Variables	TXA group	Control group	*P***
Hb (g/dl)			
Before	13.38±1.76	13.5±1.80	<0.001
After	12.45±1.79	11.99±2.11	
*P**	<0.001	<0.001	
HCT (L/L)			
Before	40.01±5.34	39.8±5.65	0.006
After	37.3±4.84	35.9±5.83	
*P**	<0.001	<0.001	
Plt (/ul)			
Before	191,384.6±58,638	192,940±57,551	0.145
After	178,750±55,845.3	176,900±55,086	
*P**	<0.001	<0.001	
Time of hospitalization (day)	3.28±0.45	4.38±0.94	<0.001$
Duration of surgery	98.11±37.11	124.00±39.12	0.001$

*Resulted from paired samples *t*-test, **Resulted from ANCOVA, $Resulted from independent samples *t*-test. Hb=Hemoglobin, HCT=Hematocrit, Plt=Platelet, TXA=Tranexamic acid, ANCOVA=Analysis of covariance

$P < 0.00$, in TXA group and $r = 0.526$, $P < 0.001$ in control group), duration of surgery ($r = 0.764$, $P < 0.001$ in TXA group and $r = 0.760$, $P < 0.001$ in control group). However, no significant correlation was observed between age and bleeding volume in both groups ($r = 0.13$, $P = 0.35$ in TXA group and $r - 0.024$, $P = 0.87$ in the control group).

We did subgroup analyses at categories of these variables. Table 3 shows the mean value of bleeding volume was significantly different in categories of prostate size and duration of surgery in both TXA and control groups. On the other hand, in each category of prostate size and surgery duration, we observed a significant difference between two TXA and control groups in terms of bleeding volume [Table 3].

DISCUSSION

The findings of the current study showed that the mean bleeding volume in the case and control groups was

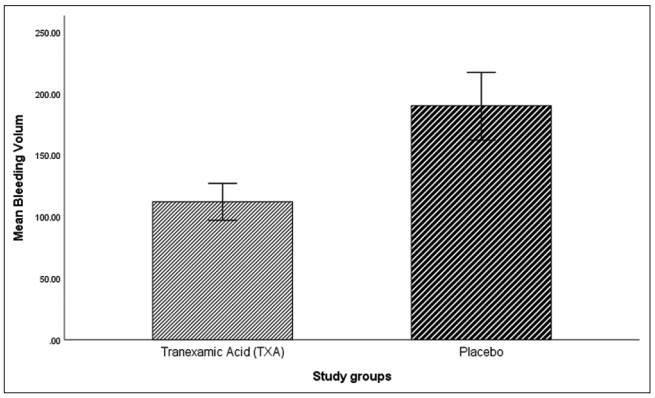

Figure 2: Mean along with 95% confidence interval for mean of bleeding volume in two groups

112.11 ± 53.5 CC and 190.00 ± 97.5 CC, respectively. In this regard, the mean bleeding in the case group was significantly lower than in the control group**.** In addition, although there was a significant difference in the mean bleeding of case and control groups in the age group more than 60 years, the mean bleeding after intervention in age <60 years was also lower than in control groups. Meng *et al*. assessed the effect of TXA in reducing perioperative blood loss in patients with BPH. In this regard, patients were intravenously administered with 1 g TXA or placebo, and observed that TXA reduced blood loss intraoperatively and 4 h postoperatively than the control group.[15] Rannikko *et al*. also reported that short-term TXA treatment significantly decreased the operative blood loss.[16] Kresimir Oremus *et al*. assessed the effect of TXA on blood loss in knee arthroplasty and reported that the combined dose of regimen seems to be more effective than single-dose local application in reducing blood loss.[9] Jean *et al*. evaluated the effect of TXA on perioperative blood loss in patients who underwent spinal fusion surgery and revealed that TXA significantly decreased perioperative blood loss in these patients.[17] Longo *et al*. evaluated the effect of TXA on perioperative blood loss in patients who underwent prostate surgery and reported that the administration of TXA decreased intraoperative blood loss and the need for transfusion.[18]

Mina *et al*. evaluated the effect of TXA in reducing bleeding in prostate surgery and revealed that TXA was effective in the prevention of perioperative blood loss than placebo in patients underwent transurethral resection of the prostate.[13] They also revealed that preventive management of bleeding with TXA was an attractive intervention due to its reasonable cost, safety, and effectiveness in decreasing perioperative blood loss.[13] Kumsar *et al*. reported that the reduced bleeding volume during surgery may lead to a better surgical situation and shorter operative time.[19] Therefore, TXA treatment may lead to reduce in irrigating fluid absorption. It seems that TXA blocked a lysine-binding site of plasminogen and inhibited its conversion to the

Table 3: Subgroup analysis for comparison of bleeding across categories of confounding variables

Bleeding	TXA group	Control group	*P**
Age (years)			
<60	104.2±46.1	182.0±84.3	0.066
>60	113.3±55.02	190.8±99.7	<0.001
*P**	0.68	0.84	
Size of prostate (CC)			
<100	86.47±40.67	162.00±84.94	<0.001
>100	160.55±40.06	255.33±96.04	<0.001
*P**	<0.001	0.001	
Duration of surgery (min)			
0-60	64.61±29.89	-	-
61-120	115.66±48.89	139.67±43.7	0.1
>120	168.88±31.00	272.1±106.07	0.01
P$	<0.001	<0.001	

*Resulted from independent samples *t*-test or Mann-Whitney *U*-test, $Resulted from Kruskal-Wallis test. TXA=Tranexamic acid

active enzyme plasmin. They also revealed that the reduced bleeding during surgery due to TXA therapy may lead to better surgical situations and shorter operative time.[19]

The findings of the current study after intervention demonstrated significantly difference between the case and control groups, considering Hb, HCT, and Plt**.** Mina *et al*. evaluated the effect of TXA in prostate surgery and revealed that the prescription of TXA did not increase the Hb values at the end of the procedure,[13] which was consistent with our study. Longo *et al*. assessed the effect of TXA on bleeding volume in prostate surgery and observed no significant difference between the intervention and control groups in terms of Hb level.[18] The finding of this study was consistent with our study. In addition, they revealed no significant difference before and after the administration of TXA regarding the Hb levels.[18] Kumsar *et al*. evaluated the effect of TXA on blood loss during TURP surgery and observed that there was no significant difference between the case and control groups regarding the serum Hb loss on the 1st postoperative day.[19] This finding was also consistent with our study. Poyrfakour *et al*. assessed the effect of TXA on Hb, HCT, and Plt levels during prostatectomy surgery and revealed that the decrease in postoperative Hb and HCT levels were lower in the intervention group than in the control group. Furthermore, the decrease in Plt level in the intervention group was significantly lower than in the control group.[20] Kim *et al*. reported that TXA reduced hematologic parameters, Hb, and Hct levels after total shoulder Arthroplasty, which was inconsistent with our study.[21] It seems that the difference between the current study with Kim and Poyrfakour studies was due to the type of surgery, and dosage of TXA.

The comparison of bleeding in two groups in terms of the length of hospitalization showed that there was no significant difference between the bleeding of two groups in terms of hospitalization length. In addition, we observed a significant difference between bleeding of case and control groups regarding the duration of surgery, for 120 min or more. Various studies were conducted regarding the comparison of placebo and case groups regarding hospitalization length, and duration of surgery;[19,22,23] however, few studies compared the bleeding volume of patients who were treated with TXA and placebo in terms of hospitalization length. However, Rannikko *et al*. assessed the effect of TXA administration in reducing the operative blood loss and revealed that the bleeding volume was not affected by the hospitalization length.[16] The finding of this study was consistent with our study. Kumsar *et al*. assessed the effect of TXA on blood loss during transurethral resection of the prostate and observed that operating time in the TXA group was significantly shorter than in the control group.[19]

Moreover, bleeding volume in the case group was significantly lower than the control group in different sizes of prostate (less and more than 100 CC), indicating no effect of the prostate size on bleeding. Kumsar *et al*. also reported that there was no significant difference between the bleeding of TXA and control groups regarding the size of prostate.[15] Therefore, according to the findings of these two studies, it seems that the size of prostate did not affect bleeding.

CONCLUSION

According to the findings of the current study, the administration of TXA led to reduce bleeding in BPH patients who underwent open prostatectomy. Furthermore, the mean Hb, HCT levels were significantly affected by TXA. TXA treatment approach also can reduce the surgery and hospitalization time effectively. TXA is recommended as effective treatment in BPH patients who underwent open prostatectomy.

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Conflicts of interest
There are no conflicts of interest.

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