

# Local Administration of Tranexamic Acid During Prostatectomy Surgery: Effects on Reducing the Amount of Bleeding

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## Abstract

**Background:** One of the issues in prostatectomy surgery is bleeding. Although tranexamic acid (TRA) is an antifibrinolytic agent for reducing bleeding, controversies surround its use.

**Objectives:** In this study, the effect of local administration of TRA on reducing bleeding during prostatectomy surgery was evaluated.

**Methods:** A total of 186 patients who underwent prostatectomy surgery were assessed in this clinical trial study. Patients were divided randomly into two groups. After prostate removal, TRA (500 mg TRA with 5 mL total volume) to the intervention group and normal saline to the control group were sprayed with the same volume. At the end of surgery, the prescribed blood bags were measured and recorded. Hemoglobin and platelet levels were recorded 6 hours after the test. Moreover, the amounts of blood inside the blood bags in the first 24 hours, the second 24 hours, and the total length of hospital stay were recorded and compared in each group.

**Results:** By comparing the measured values before and after surgery, we found that the amounts of hemoglobin, hematocrit, and platelet decreased. The mean blood loss in the intervention group was recorded at 340 mL and that in the control group was 515 mL. The maximum bleeding in the control group was almost twice as much as that in the intervention group. Blood loss in the intervention group with the administration of TRA was significantly lesser than that in the control group ( $P = 0.01$ ). The decrease in platelet level in the intervention group was significantly lower than that in the control group ( $P = 0.03$ ).

**Conclusions:** The present study showed that local administration of TRA significantly reduces bleeding after prostatectomy surgery and is effective in preventing postoperative hemoglobin decrease.

**Keywords:** Tranexamic Acid, Bleeding, Prostatectomy

## 1. Background

Benign prostatic hyperplasia (BPH) is a major public health problem affecting men older than 50 years of age (1, 2). In 2008, BPH was the second most frequently diagnosed cancer in men worldwide with an estimated 899,000 new cases (13% of all new cancer cases) (3-7). These tumors can be managed in different ways. Despite the introduction of laparoscopy (including robotic-assisted approaches), open radical retropubic prostatectomy is still the standard surgical treatment for localized prostate cancer (4, 7-11). The historical gold standard of transurethral resection of prostate (TURP), which is an effective procedure, is still associated with the risk of intraoperative and postoperative bleeding (2, 12-14).

Factors that influence perioperative and postoperative blood loss include prostate weight, weight of the resected tissue, operating time, preoperative urine culture, preoperative finasteride treatment, use of acetylsalicylic acid, type of anesthesia, patient age, and blood pressure although some of these associations remain controversial (2).

Consequently, patients undergoing open radical prostatectomy usually require blood transfusion to restore tissue oxygenation (4, 15, 16). Nonetheless, blood transfusions have rare but potentially serious adverse effects, including hemolytic reactions (acute and delayed), acute lung injury, coagulopathic complications from massive transfusion, mistransfusion, and non-immune hemolysis and transfusion-associated infections (4, 17-19).

Additionally, as blood is a scarce resource, substantial economic costs are associated with allogeneic transfusions (4, 20).

Recently, a growing body of evidence has indicated that tranexamic acid (TRA) is an effective agent for reducing blood loss in different surgeries (2, 21, 22). In the literature, 16 studies evaluating the use of TRA in cardiac surgery, 6 trials in upper gastrointestinal bleeding, 3 trials in oral surgery, 2 trials in orthopedic surgery, X trials in gynecological surgery, and several other trials evaluating the use of TRA in other indications were included (23).

TRA, a synthetic derivative of the amino acid lysine that exerts an antifibrinolytic action, is the standard treatment used to reduce the rate of perioperative and intraoperative transfusion by preventing the breakdown of fibrin and stabilizing blood clots (2, 4, 23-26). Treatment with TRA does not seem to adversely affect mortality and morbidity (4, 27). Moreover, TRA is less expensive than other hemostatic drugs (4, 28).

## 2. Objectives

We conducted a randomized controlled trial to assess the efficacy of TRA in reducing the amount of bleeding and the rate of blood transfusion in patients undergoing prostatectomy and the long-term safety of this treatment.

## 3. Methods

Approval was obtained from the ethics committee of Tehran University of Medical Sciences. After conducting preliminary studies and applying the inclusion and exclusion criteria, patients who were scheduled for elective prostatectomy were enrolled in the clinical trial. The following patients were excluded from the study: using anticoagulant drugs such as aspirin and dipyridamole, with high PT (prothrombin time) and PTT (partial thromboplastin time) for any reason, with any history of thrombotic events, with a history of bleeding disorders, with chronic kidney disease (serum creatinine > 180  $\mu\text{mol/L}$ ), with cardiovascular disease treated with drug eluting stent, with atrial fibrillation, with congenital or acquired thrombophilia, with known or suspected allergy to TRA, and undergoing general or epidural anesthesia with the acknowledgment of the supervising physician.

The patients were divided randomly into two groups. After prostate removal, TRA to the intervention group (500 mg TRA with 5 mL total volume) and normal saline to the control group were sprayed with the same volume and speed. In all patients, hemoglobin, platelet, and hematocrit were measured and recorded the day before surgery and 24 hours after surgery.

All patients underwent spinal anesthesia and were operated by the same surgical team. Surgeon and patient were unaware of the study and intervention. At the end of surgery, another colleague counted the prescribed blood bags, and the hemoglobin and platelet levels were measured and recorded 6 hours after the test. In addition, the amount of blood inside the blood bags was recorded and compared in the two groups in the first 24 hours, the second 24 hours, and the total length of hospital stay. The number of transfused blood bags in 24 hours after surgery was recorded for each patient.

After the completion of forms for all patients, information was entered and analyzed using SPSS software. Qualitative variables were analyzed by the chi-square test and quantitative variables by the t-test. P value was considered statistically significant at  $P < 0.05$ . The level of significant in all testing was 95%.

## 4. Results

A total of 186 patients were finally assessed. Patients in the intervention group were aged 49 - 86 years ( $9.9 \pm 67.7$ ), and those in the control group were aged 51 - 88 years ( $8.9 \pm 64.9$ ). Patients in both groups were in class I and II ASA (American statistical association) on average. Duration of the surgery was reported at 1 h and 15 min in the intervention group and 1 hour and 20 minutes in the control group. Weight of patients in both groups was in the range of 60 - 80 kg with no significant difference. Prostate weight in all patients was 70 - 90 g. No statistically significant differences were found between the two groups in age, prostate size, and duration of surgery.

Hemoglobin, hematocrit, platelets, and bleeding were measured in two innings before and after surgery and then recorded. Comparison of the measured values before and after surgery indicated that the amount of hemoglobin, hematocrit, and platelets all declined. According to the results of the statistical analysis, the intervention group had a mean blood loss of 340 mL and the control group had a mean blood loss of 515 mL. Despite the equality of the minimum amount of bleeding in both groups, the maximum amount of bleeding in the control group was found to be almost twice as much as that in the intervention group. The low blood loss in the intervention group with the administration of TRA after prostatectomy was statistically significant ( $P = 0.01$ ).

The decrease in hemoglobin and hematocrit levels after surgery were lesser in the intervention group than in the control group, and this difference was statistically significant ( $P = 0.04$ , respectively, and  $P = 0.05$ ). In addition, the decrease in platelets level in the intervention group was also significantly lower than that in the control group

(P = 0.03). These considerable reasons can account for the lower rate of bleeding in the intervention group with the TRA prescription than in the control group.

After surgery, none of the patients who received TRA suffered from vascular events, such as thromboembolism, pulmonary embolism, CVA (cerebrovascular accident), MI (myocardial infarction), DVT (Deep vein thrombosis), etc. Only one patient suffered from severe bleeding during surgery which led to increased heart rate and reduced blood pressure.

As previously mentioned, the amount of hemoglobin reduction, the amount of bleeding after surgery, and the subsequent need for pack cell transfusion were lower in the intervention group than in the control group. In the control group, five patients had to undergo pack cell transfusion, whereas none of the patients in the case group received pack cell transfusion.

Table 1. Variable of Intervention Group

Variable	Minimum	Maximum	Mean ±
<b>Pre-operation</b>			
Hb, g/dL	11.9	16.8	14.24 ± 1.54
HCT	36.3	53	42.53 ± 3.89
PLT	153	340	217.69 ± 44.11
<b>Post-operation</b>			
Hb, g/dL	9.9	15.6	12.31 ± 1.62
HCT	31	59	38.14 ± 6.46
PLT	131	308	197.96 ± 40.24
<b>Bleeding</b>	100	750	340 ± 152.1

Table 2. Variables of the Control Group

Variable	Minimum	Maximum	Mean ± SD
<b>Pre-operation</b>			
HbHb, g/dL	11.8	17.2	14.39 ± 1.6
HCT	34.8	54	42.88 ± 5.09
PLT	120	370	206.4 ± 54.31
<b>Post-operation</b>			
HbHb, g/dL	10.1	16.6	12.43 ± 1.73
HCT	22.9	58	37.38 ± 7.34
PLT	107	363	187.53 ± 57.54

Table 3. Variable Difference Between the Two Groups

Variable	Mean ± SD
<b>ΔHb</b>	
Case	1.9267 ± 1.02877
Control	1.9533 ± 1.25817
<b>ΔHCT</b>	
Case	4.5867 ± 4.12312
Control	5.1089 ± 5.28638
<b>ΔPLT</b>	
Case	19.73 ± 26.042
Control	15.87 ± 17.449

### 5. Discussion

To the best of our knowledge, only one study has ever used intraoperative IV TRA to reduce the amount of bleeding in prostatectomy.

Crescenti (4) evaluated the effect of TRA on blood loss after prostatectomy in 200 patients and found that 34% of those in the TRA group and 55% of those in the control group received blood. According to the results, a 232 mL bleeding reduction was observed in the TRA group. These results are close to findings obtained from the current study. In other studies, topical TRA was used to control local bleeding. For example, the topical use of TRA was found to control bleeding in patients with bleeding disorders undergoing gynecologic surgery (29). The effects of topical application of this drug was positively considered in reducing bleeding after tooth extraction in children with hemophilia and after orthopedic surgery (25, 30). Fawzy found that the topical use of TRA in patients undergoing coronary artery bypass significantly led to low blood loss with no additional adverse effects (31). Krohn et al. (32) evaluated the effects of topical use of TRA on the amount of bleeding after lumbar vertebra fixation surgery and fibrinolysis of drainage blood in 30 patients. According to the results, the mean blood loss was reduced by half from 525 mL to 252 mL (P = 0.02) in the TRA group. Abrishami et al. (33) found that the topical application of anti-fibrinolytic agents, particularly aprotinin or TRA, reduced the amount of bleeding in the first 24 hours after surgery and led to transfusion saving of one unit of isogroup blood for each patient. De Bonis showed that topical use of TRA (1 g of TRA diluted in 100 ml normal saline topically) in the pericardium after CABG (coronary artery bypass graft) in patients undergoing primary coronary artery bypass caused a significant reduction of postoperative bleeding compared with the placebo (34). Similar results were ob-

tained in the present and other studies.

Postoperative anemia is also a major problem that contributes to increased morbidity and mortality (35) and prolonged hospitalization (36). Previous studies showed that topical application of TRA decreased the post-operative blood hemoglobin reduction. Seo et al. (36) reported that intravenous administration of TRA was more effective than its topical application in the prevention of blood hemoglobin reduction.

However, some studies produced opposite conclusions. Yasim et al. (37) showed that applying topical aprotinin and TRA reduced postoperative bleeding during heart surgery, but this difference was not statistically significant. Moreover, the difference between aprotinin and TRA in decreasing blood transfusion demand was not statistically significant.

The current study chose to evaluate TRA as recent studies have demonstrated that the local use of either TRA or aprotinin could practically decrease the rate of post-cardiac surgery bleeding. Although the strength of local administration of TRA has been observed to be the same as that of local administration of aprotinin in decreasing bleeding, the former is potentially more safer and inexpensive than the latter (38). However, not all researchers agree on this finding (37). Nevertheless, note that aprotinin may be more preferable to TRA in surgeries such as cardiac surgery, which has a high risk of bleeding (27). TRA comprises small molecules (molecular weight 157 Daltons) that interfere with the connection point of lysine to plasminogen and their product of transforming to plasmin. It exclusively prevents plasmin from accessing fibrin and has no other direct effect on hemostasis. Conversely, aprotinin, which is a non-exclusive serine inhibitor, directly inhibits plasmin in low density and makes the contact phase of the inner route of hemostasis easy in high density, thus resulting to minimal anti-coagulation effects (38). In the mechanism of the local administration of TRA, a 150% increase was observed in the density of plasmin/alpha 2-antiplasmin and D-dimer in the drainage blood of the TRA group 1 hour after surgery. The increase was 320% and 260% in the observed group, respectively. No side effects were reported in the local use of this type of medicine. Eventually, the local use of antifibrinolytic was concluded to reduce post-surgery bleeding and the necessity for blood transfusion in patients undergoing on-pump cardiac surgery (31). A new meta-analysis on the use of transamin for decreasing bleeding volume was published (39). In this study, platelet and coagulation disorders simultaneously affect the whole bleeding volume. For instance, hypotensive anesthesia, correct position of the patient and patient volume correction greatly affect the decreasing waste bleeding, which needs to be evaluated in future studies.

## 5.1. Conclusion

Taking the effects of TRA in preventing postoperative hemoglobin into account, the intravenous administration of this drug is more effective than topical treatments used in surgery. The most common surgical side effect of prostatectomy is bleeding, but any attempt to use hemostatic agents to control it has not been successful. TRA is a safe and effective drug for reducing bleeding during and after surgery in prostatectomy and is recommended for routine use. Future studies can perform ROTEM (rotational thromboelastometry) and measure the intraoperative hemoglobin level.

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