

Tranexamic acid is beneficial for reducing perioperative blood loss in transurethral resection of the prostate

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Abstract. The aim of this randomized controlled trial was to evaluate the effect of tranexamic acid (TXA) on postoperative blood loss during transurethral resection of the prostate (TURP) for benign prostatic hyperplasia (BPH). A total of 60 patients with BPH and undergoing TURP were randomized into TXA and control groups. Patients were intravenously administered 1 g TXA or placebo (0.9% sodium chloride solution), respectively, after the induction of anesthesia for TURP. Intraoperative and postoperative bladder irrigation volumes and blood loss volumes were compared between the two groups. Coagulation function (measured by prothrombin, activated partial thromboplastin and thrombin time and fibrinogen levels) was measured before the operation and at 4 h post-operation. Complications from thromboembolic events, such as lower-limb and pulmonary embolisms, were also noted. The TXA group had significantly decreased blood loss intraoperatively and at 4 h postoperatively compared with the control group ($P < 0.05$). The 24 h postoperative blood loss and coagulation function of the two groups were not significantly different. No thromboembolic events or other complications occurred in either group. In conclusion, a preoperative single dose of TXA was indicated to reduce perioperative blood loss in TURP without a notable increase in thrombosis risk.

Introduction

Benign prostatic hyperplasia (BPH) is among the most common diseases in elderly patients with urinary tract obstructions (1). BPH is a nonmalignant enlargement of the prostate gland caused by cellular hyperplasia of the glandular and stromal elements; BPH leads to troublesome lower urinary tract symptoms in some men. Transurethral resection of prostate (TURP) is one of the most common and well-developed technologies used to

treat BPH. It is recognized as the gold standard for surgical BPH treatments (2) and has replaced traditional open surgeries. However, because the surrounding prostate tissue contains large venous sinuses, these can easily be breached during the surgery, which can cause complications such as bleeding and TURP syndrome (3); in fact, hemorrhage is the most common complication of this type of surgery (4). Additionally, hemorrhage can cause water poisoning, and severe cases can lead to hemorrhagic shock and affect patient prognoses (5).

Tranexamic acid (TXA) is a type of synthetic fibrinolysis resistance drug that has been demonstrated to be effective for decreasing blood loss in multiple surgical procedures (6,7). TXA has been used across a wide range of clinical setting to control hemorrhaging in cardiac surgery (8), liver transplantation (9), urological surgery (2) and orthopedic surgery (10).

The aim of this prospective randomized controlled study was to evaluate the effect of TXA on perioperative blood loss during TURP. Additionally, the safety of TXA use during TURP surgery was evaluated and discussed.

Materials and methods

Patient recruitment. This research was approved by the Dalian Medical University Second Affiliated Hospital Ethics Committee (Dalian, China). Informed consent was obtained from all patients. A total of 60 male patients diagnosed with BPH and undergoing TURP were recruited between January 2012 and February 2013 based on the following inclusion criteria: American Society of Anesthesiologists classification I-III; age, 55-85 years; normal preoperative hemoglobin concentration; and an operative time of 1-3 h. The patients were randomized by medical record number; odd numbers were assigned to the TXA group ($n=30$) and even numbers were assigned to the control group ($n=30$). The TXA and control groups were intravenously administered with 1 g TXA (Wuhan Aimin pharmaceutical Co., Ltd., Ezhou, China) in 200 ml saline or a placebo (an equal volume of saline only), respectively, after induction of anesthesia. All surgeries were performed by the same surgeon. The following examinations were performed before surgery: A routine blood examination and urine test, a digital rectum examination, transrectal ultrasound, a test for prostate-specific antigen levels, urodynamics and international prostate symptom score assessment. The exclusion criteria were as follows: Preoperative heart and cerebrovascular diseases, renal insufficiency, kidney stones,

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high risk or a history of thrombosis, long-term anticoagulant therapy, preoperative long-term bed confinement, prostate cancer diagnosis, blood coagulation dysfunction. Patients were also excluded if they had taken 5-a reductase inhibitors, aspirin or warfarin prior to surgery.

Experimental protocol. All of the operations were performed by the same surgeon with the patients under general anesthesia. To induce anesthesia, patients were intravenously administered with 0.05 mg/kg midazolam (Jiangsu Enhua Pharmaceutical Co., Ltd., Xuzhou, China), 0.4 µg/kg sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China), 0.3 mg/kg etomidate (Jiangsu Enhua Pharmaceutical Co., Ltd.) and 0.2 mg/kg cisatracurium besylate (Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China). After administering oxygen for 2-4 min, a laryngeal mask was inserted. During the intraoperative period, propofol and remifentanyl were continuously administered to maintain a bispectral index value of 50±5. The intraoperative infusion volume and infusion speed were adjusted by central venous pressure. TXA group patients received 1 g TXA in 200 ml of normal saline after anesthesia induction, while the control group patients received a placebo (200 ml normal saline) after anesthesia induction. The medication drip speed was 20-30 drops/min. The experimental drug was administered by an anesthesia nurse, and the surgeon was blinded to the patient groups.

Measurement of experimental outcomes. The intraoperative and postoperative blood loss volumes for each patient were measured by a nurse who was blinded to the patient groups. Bladder irrigation fluid was collected at three time points: Immediately following the operation (T₁) and 4 h post-operation (T₂) and 24 h post-operation (T₃). The total volume was measured and 5,000 U heparin was added to the flushing fluid containers. After the fluids were fully mixed, 5-ml samples were drawn and subjected to cyanide methemoglobin spectrophotometer colorimetry to evaluate hemoglobin (HB) concentration at a wavelength of 540 nm. Blood loss was then calculated using the following formulae: i) HB concentration in washing liquid (g/l)=absorbance of fluid x 367.7; ii) Bleeding volume (ml)=HB concentration in washing liquid (g/l) x Rinse volume (ml)/Preoperative hemoglobin concentration (g/l) (11).

Coagulation functions (including prothrombin, activated partial thromboplastin and thrombin clotting times and fibrinogen level) of the two groups were measured pre-operation and at 4 h post-operation. Any signs of thromboembolic events, including lower-limb and pulmonary embolisms, were noted.

Statistical analysis. The statistical analyses were performed using SPSS 18.0 (SPSS, Inc., Chicago, IL, USA). All data are presented as the mean ± standard deviation. The analyses were performed using two-tailed t-tests. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. No significant differences were observed between the two groups with regard to age, height, weight, prostate size, postoperative bladder washing time, surgery duration or length of hospital stay (Table I). In

Table I. Perioperative patient data.

Parameter	Tranexamic acid	Control
Age (years)	71.4±5.4	70.7±8.5
Weight (kg)	75.0±8.9	71.4±3.6
Preoperative hemoglobin (g/l)	137.9±10.7	143.1±8.7
Postoperative hemoglobin (g/l)	124.0±10.4	121.7±14.7
Size of the prostate (ml)	73.3±8.3	66.6±3.9
Postoperative bladder irrigation time (h)	25.0±2.2	24.3±2.3
Duration of operation (min)	101.7±8.9	89.7±5.2
Length of hospitalization (days)	15.9±5.2	13.9±3.9

the TXA group, the preoperative and postoperative hemoglobin concentrations were 137.9±10.7 and 124.0±10.4 g/l, respectively. In the control group, the preoperative and postoperative hemoglobin concentrations were 143.1±8.7 and 121.7±14.7 g/l, respectively. There were no significant differences in hemoglobin concentration between the two groups at either time point. In summary, no significant difference in the basic conditions were identified between the two groups of patients.

Coagulation function. No significant difference was observed in the coagulation function of the two groups. There was no evidence of lower-limb deep vein thrombosis or pulmonary embolism in either group (Table II).

Bladder irrigation volume. No significant difference was observed in the bladder irrigation volume of the two groups at any of the three time points (T₁, T₂ and T₃) (Table III).

Blood loss. The blood loss at T₁ and T₂ in the TXA group was 102.0±11.4 and 61.9±6.1 ml, respectively. In the control group, the blood loss at these times was 303.6±24.8 and 84.8±15.2 ml, respectively. According to these findings, hemoglobin losses at T₁ and T₂ were significantly lower in the TXA group compared with the control group (P=0.002 and P=0.035, respectively; Table IV). Blood loss at T₃ was not significantly different between the two groups.

Discussion

The results of the current study indicated that TXA could reduce intraoperative and 4 h postoperative blood loss resulting from TURP surgery, but it had no significant impact on 24 h postoperative blood loss. Kumsar *et al* (12) reported that 10 mg/kg TXA administered 30 min before surgery significantly reduced hemoglobin loss per 1 g prostate tissue. Rannikko *et al* (13) randomly selected 136 patients who were undergoing TURP surgery and administered 2 g TXA or placebo preoperatively. It was observed that 50% of the TXA group showed reduced intraoperative bleeding (13). In the current study, it was observed that in the TXA group, intraoperative blood loss was significantly lower compared with the control group. This suggests that TXA could help to

Table II. Coagulation rates before and after transurethral resection of the prostate (n=30).

Group	Pre-operation				4 h post-operation			
	PT (sec)	APTT (sec)	FB (g/l)	TT (s)	PT (sec)	APTT (sec)	FB (g/l)	TT (sec)
Tranexamic acid	12.6±0.7	35.8±3.1	4.1±1.3	16.3±1.1	12.8±0.7	36.0±3.1	4.0±1.3	16.3±1.4
Control	12.4±0.7	35.2±3.0	3.9±1.3	17.1±1.2	13.0±0.8	35.6±3.2	3.8±1.0	17.5±1.5

PT, prothrombin time; APTT, activated partial thromboplastin time; FB, fibrinogen level; TT, thrombin clotting time.

Table III. Bladder irrigation volume (l) at three time points after transurethral resection of the prostate.

Group	T ₁	T ₂	T ₃
Tranexamic acid	27.5±1.8	0.7±0.1	18.3±0.7
Control	25.7±0.9	0.8±0.1	17.6±0.8

T₁, the intraoperative operation; T₂, 4 h post-operation; T₃, 24 h post-operation.

Table IV. Blood loss (ml) at three time points after transurethral resection of the prostate.

Group	T ₁	T ₂	T ₃
Tranexamic acid	102.0±11.4 ^a	61.9±6.1 ^a	63.9±5.2
Control	303.6±24.8	84.8±15.2	77.4±5.0

T₁, the intraoperative operation; T₂, 4 h post-operation; T₃, 24 h post-operation. ^aP<0.05 vs. control.

reduce patient trauma and decrease the intraoperative blood transfusion risk.

The prostate has a rich blood supply, and the surrounding tissue contains large venous sinuses (4). When an electric scalpel is used to remove prostate tissue, the electric knife squeezes the venous sinuses, which releases a large number of fibrinolytic enzymes into the blood and activates the fibrinolysis system (14). The affected fibrin then dissolves into soluble fibrin degradation products, which causes bleeding (15).

TXA is a synthetic anti-fibrinolytic with a chemical structure similar to that of lysine (16,17). It can restrain the fibrinolytic enzyme adsorption of fibrin and promote blood clot formation; thus, it has hemostatic effects during TURP surgery (18,19). The half-life of TXA is approximately 3 h if the intravenous injection dosage is 15 mg/kg (4). According to the manufacturer's specification, at 1 h, the blood concentration is 20 µg/ml, and at 4 h, the blood concentration is 5 µg/ml. In the current study, TXA was administered immediately after anesthesia, and the surgery was conducted over the following 1-3 h. It was observed that TXA had the greatest hemostatic effects during surgery and at 4 h post-operation. There is no single recommended mode of delivery or dosage for TXA

when it is applied in a variety of surgical procedures (8,20,21). For prostate surgery, the manufacturer suggests reducing the drug dosage in elderly patients. In this study, 1 g of the drug was used, and the drip speed was controlled, which not only achieved good hemostatic effects with no complications, but also demonstrated that this method was reasonable and effective.

Given TXA's effects on intraoperative blood loss, its influence on postoperative blood loss was also investigated in the current study. Previous studies have reported that postoperative bleeding during TURP surgery is associated with excessive fibrinolytic system activation, which TXA reduces to achieve a hemostatic effect (7,22). When the statistical results were combined, the postoperative bladder irrigation times for the two patient groups, which were operated on by the same surgeon, were not significantly different. After TXA administration, however, the blood loss at 4 h post-operation was significantly reduced, indicating that TXA improved stypic effects within 4 h after surgery. However, TXA had no significant effect on blood loss 24 h after surgery. The authors of the current study speculated that, without pain stimulation for prostate tissue resection, catheter indwelling would not have lead to differences in blood loss being identified between the two groups within the 24 h of the surgery.

Rannikko *et al* (13) used TXA on the day of surgery and at day 1 post-TURP surgery and found that the bladder irrigation volume of the TXA group was significantly reduced compared with the control group. In the current study, the intraoperative and 24 h postoperative bladder irrigation volume of the TXA group (27.5±1.76 and 18.26±0.70 l, respectively) was slightly higher than that of the control group (25.7±0.91 and 17.6±0.77 l, respectively), but the difference was not statistically significant. Therefore, it cannot be concluded with certainty that TXA had any effect on the postoperative bladder irrigation fluid volume.

Given that the availability of aprotinin, a natural anti-fibrinolytic agent, is restricted in China, more attention regarding the side effects of such drugs is needed. Lowe *et al* (23) demonstrated that an age >40 years, surgical time >30 min, pelvic surgery history and a history of deep vein thrombosis combined with heart failure and cancer increased the perioperative thrombosis risk. Thromboelastography (TEG) is a technology used to monitor the fibrinolytic system (24-26). It can dynamically monitor the level, speed and degree of activity of the fibrinolytic system and of blood clot-forming tendencies between the preoperative and postoperative periods; however, it is not often used in clinical applications. Faraoni *et al* (27) used TEG to measure fibrinolysis during cardiac surgery in an

experimental group (two doses of TXA) and a control group (normal saline), but the results were not statistically significant. Chakravarthy *et al* (28) used TEG to compare the influence of TXA and hydroxyethyl starch on extracorporeal circulation blood loss during heart surgeries; however, these results were not statistically significant either.

Due to limited funding, TEG could not be used in this study. Instead, prothrombin, activated partial thromboplastin and thrombin time and fibrinogen levels were measured directly in the two groups preoperatively and at 4 h post-operatively. The development of lower-extremity deep vein thromboses or pulmonary embolisms after seven days was also monitored. Compared with younger patients, elderly patients are usually less physically active on a daily basis, and their blood viscosities are higher; therefore, the lithotomy position used during surgery can be a risk factor for thrombosis (23). However, in the current study, the preoperative and 4 h postoperative coagulation functions were not significantly different. Furthermore, none of the 60 patients had deep vein thromboses or pulmonary embolisms within seven days post-operation, suggesting that TXA treatment does not result in thrombosis.

Previous results have demonstrated that TXA can cause complications, such as postoperative central nervous system convulsions, particularly in relation to the dosage (29). Currently, these findings have only been reported in cardiac surgery patients, and such complications are likely to be the result of TXA blocking GABA receptors in nerve cells (30-34). One study has also reported that the risk of epilepsy is increasing in children who have undergone heart surgery involving TXA treatment (35). Although TURP surgeries have not yet been reported to have such complications, further studies on the postoperative neurological complications of TXA are required.

In conclusion, the current study indicates that the preoperative use of 1 g TXA administered immediately after anesthesia can reduce intraoperative and 4 h postoperative blood loss for TURP surgery, with no adverse side effects.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JYX contributed to the conception and design of the study. QQM performed the data collection. QQM and NP recruited the patients. QQM, NP and NL performed the spectrophotography and data analysis, and wrote the manuscript. QQM and JYX interpreted the data. JYX and NP revised the article.

Ethics approval and consent to participate

The current study was performed in the laboratory of the Second Affiliation Hospital of Dalian Medical University and supported by the National Natural Science Foundation of China (grant no. 2012-044 given to JYX). Informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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