Original Article

Efficacy of tranexamic acid in decreasing primary hemorrhage in transurethral resection of the prostate: A novel combination of intravenous and topical approach

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Abstract

Background: Transurethral resection of the prostate (TURP) is the gold standard for benign prostatic enlargement; however, hemorrhage still remains one of the major complications.

Objective: The primary aim of this study was to evaluate the effect of tranexamic acid (TXA) in reducing intraoperative blood loss and need for blood transfusion. Secondary parameters compared were operating time, volume of irrigation fluid used, and reduction in hemoglobin concentration.

Subjects and Methods: A total of 70 eligible patients undergoing TURP were randomized based on computer generated table into two groups. The study group (1) received IV TXA 500 mg after induction of anesthesia and 500 mg in each irrigation fluid bottle (dual mode) and the control group (2) received none.

Results: The mean age (68.20 vs. 66.5 years), prostate size (57 vs. 51 g), and preoperative hemoglobin (13.3 vs. 13.5 g/dl) were similar between the groups. Intraoperative blood loss in the TXA group was found to be significantly reduced (174.60 ± 125.38 ml vs. 232.47 ± 116.8; $P = 0.04$). Blood transfusion was required in 2.8% of cases as compared to 14.2% in controls. Operating time, volume of irrigation fluid, and postoperative reduction of hemoglobin were not significant between the groups. No complications were observed in both groups.

Conclusion: In this study, we observed that TXA, when used as a combination of Intravenous and topical route, effectively reduced intra-operative blood loss and the need for transfusion.

Keywords: Benign prostatic hyperplasia, intraoperative hemorrhage, tranexamic acid, transurethral resection of prostate

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common conditions causing lower urinary tract symptoms (LUTS) in elderly males.[1] The histologic prevalence of BPH is approximately 20% for men in their 40s, rising to 80%–90% for men in their 70s and 80s.[2] Many newer minimally invasive nonlaser and laser techniques have been developed for resection; however, transurethral resection of the prostate (TURP) remains the gold standard.[3]

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The prostate has a dense vascular supply with large venous sinuses, which are easily breached during surgery, which leads to bleeding, which in fact, is the most common complication of TURP and might require transfusion in up to 7% of cases.[4] Hemorrhage may even cause increased water reabsorption causing life-threatening TUR syndrome.[4] Complementing the above, urothelium and prostatic tissue are rich in plasminogen activators, which following surgical trauma in combination with high urokinase levels in the urine causes lysis of the clots or fibrinolysis.[5]

Of many interventions to reduce this perioperative blood loss use of antifibrinolytics has shown some promise. Tranexamic acid (TXA) has a plasminogen-binding potency 6–10 times greater than other medications of the same class and blocks fibrinolysis through the competitive inhibition of plasminogen activation into plasmin, thus reducing bleeding during surgeries.[6] A systematic review of the literature of TXA in patients undergoing elective surgery (cardiac, hepatic, thoracic, and orthopedic surgery) demonstrated that TXA significantly reduced the need for perioperative transfusions. However, there remains a possible risk of thromboembolism (TE). The topical application of TXA has also been used in various surgeries such as dental,[7] cardiac,[8,9] and spinal surgeries.[10] It is less absorbed topically; therefore, the topical application would reduce the risk of TE along with increased effectiveness for reduction in blood loss.

The primary aim of this study was to evaluate the effect of TXA in reducing intraoperative blood loss and the need for blood transfusion when applied both intravenously and in irrigation fluid. In addition, comparison of other parameters, including operating time, volume of irrigation fluid used, and reduction in hemoglobin concentration were made.

SUBJECTS AND METHODS

It was a prospective randomized comparative interventional study and was carried out in the Department of Urology between January 2019 and November 2019 after approval by the Ethics committee (approval number: 967 MC/EC/2019). After informed consent, all individuals, aged 40–80 years, with bothersome LUTS and proven prostatic enlargement based on digital rectal examination and abdominal ultrasonography were included. Exclusion criteria included history or evidence of prostate disease other than BPH, previous prostate surgery, treatment with any 5 Alpha reductase inhibitors within 12-months, treatment with anti-platelets, or anticoagulants in the perioperative period, and severe medical conditions such as liver disease, bleeding disorders, and unstable cardiovascular problems.

A total of 70 patients were eligible and included in the study. They were randomized based on computer generated randomized table into two groups of 35 each as study (group 1) and control (group 2). The study group (1) received IV TXA 500 mg after induction of anesthesia and 500 mg in each irrigation fluid bottle of 3 L (maximum up to 2 g) and the control group (2) received none. TURP was done using a continuous flow 26 Fr bipolar resectoscope, and all the surgeries were performed by the expert surgeons under spinal anesthesia. 0.9% Normal Saline was used as irrigation fluid. Cautery settings were used as 200 watt (W) and 120 W for cutting and coagulation, respectively. Cases with any intraoperative event that lead to early abortion of the procedure like capsular perforation were not considered for the study.

The doses of TXA chosen for the current investigation were based on previous studies of intravenous TXA in patients undergoing open surgeries showing efficacy with doses of 15–20 mg/kg.[11] Accordingly, Group 1 received 500 mg IV and 500 mg in each irrigation bottle up to 3 bottles. The rate of irrigation required for good vision is approximately 300 ml/min for which irrigation bottle is placed at the height of 60 cm. The rate of fluid absorption at this level is approximately 20 ml/min, which is approximately 6.6%.[12] Hence, the actual TXA dose absorbed would be just 6.6% of the total dose delivered in irrigation.

Serum hemoglobin was measured preoperatively and 24 h after surgery. The volume and hemoglobin concentration of irrigation fluid and duration of resection were also noted. Operating time was defined as the start of resection until hemostasis was complete. All resected tissue was sent for pathological evaluation.

Blood loss was calculated as follows:

$$\text{Total blood loss (L)} = \frac{(\text{Total irrigation used (L)} \times \text{Hemoglobin concentration of irrigation fluid (g/dl)})}{\text{Hemoglobin concentration (g/dl)}}$$

The statistical analyses were performed using SPSS 24.0 (SPSS, Inc., Chicago, IL, USA). All data are presented

as the mean ± standard deviation. Differences between groups were analyzed with the two-tailed two-sample *t*-test. Finally, correlations were assessed using Pearson correlation coefficient®. $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

A total of 35 patients treated with TXA and 35 control patients were taken. In group 1, of whom the average age was 68.20 years, median prostate weight measured by abdominal ultrasound was found to be 56.87 g (24.5–99.5 g). The average age of the control group was 66.51 years, and median prostate weight was 51.20 g (24.0–90.0 g). Mean preoperative hemoglobin in Group 1 and 2 were 13.34 and 13.56. No statistical difference was found in patient characteristics [Table 1].

The mean decrease in serum hemoglobin after 24 h of surgery in the TXA group was found to be 1.31 g/dl and was 1.40 g/dl in the control group. Even if there was an absolute decrease in hemoglobin concentration between the two groups, it was not statistically significant ($P = 0.722$) [Table 2].

According to the hemoglobin concentration in irrigating fluid, the mean blood loss in the TXA group was 174.6 ± 125.38 ml as compared to 232.47 ± 116.8 ml in the control group. This absolute decrease in blood loss in group 1 was also found to be statistically significant ($P = 0.04$) [Table 2].

The total amount of irrigation fluid used, operation time, and days of postoperative hospitalization were compared in TXA and control groups. The average irrigation fluid used during TURP was 14.9 L in TXA and 15.5 L ($P = 0.703$) in control groups. The duration of the operation was 56.71 min in the TXA given and 54.5 min in the control group ($P = 0.55$). The duration of hospitalization was the same in both groups ($P = 0.733$) [Table 2]. Thus, according to these findings, no significant difference was found between the TXA group and the control group in regard to operating time, irrigation fluid volumes, and hospitalization postsurgery.

According to Pearson correlation analyses, the prostate size was found to be an independent variable for blood loss [Table 3].

Blood transfusion was required 1 of 35 (2.8%) cases in TXA group, whereas it was required in 5 out of 35 (14.2%) cases in the control group. Transfusion criteria were either blood loss of >450 ml or postoperative Hb <10 mg/dl.

On subgroup analysis, a statistically significant reduction in blood loss was found when TXA was used in larger prostate sizes [Table 4].

DISCUSSION

BPH is one of the most common causes of LUTS in the elderly and for relieving bladder outlet obstruction in men with BPH TURP has been the gold standard. Over the years, this procedure has undergone various technological advances and improvements; however, blood loss still remains a problem. Significant blood loss may cause hemodynamic instability and the need for blood transfusion, particularly in patients with large prostates.[13] Hematuria and clot retention after TURP might prolong the hospital time and may even necessitate re-operation.[13] Transfusion rates in the current literature are 0.4%–7.1%.[4]

Perioperative TURP-associated blood loss has been correlated with an increase in urinary fibrinolytic activity. Intravenous TXA has been shown to reduce this fibrinolysis, thereby preventing clot dissolution and decrease bleeding.[6] TXA has

Table 1: Patients characteristics

Variable	Group 1	Group 2	*P*
Age (years)	68.20±8.49	66.51±9.38	0.43
Prostate (g)	56.87±14.91	51.20±17.03	0.14
Preoperative Hb (g/dl)	13.34±1.71	13.56±1.59	0.59

Hb: Hemoglobin

Table 2: Comparison of outcomes and secondary parameters in treatment and control group

Variable	Mean±SD		*P*
	Group 1	Group 2	
Hb loss at 24 h (mg/dl)	1.31±0.95	1.4±1.12	0.722
Intraoperative blood loss (ml)	174.60±125.38	232.47±116.80	0.04
Irrigation fluid volume (L)	14.929±6.922	15.486±5.103	0.703
Operating time (min)	56.714±16.085	54.429±15.754	0.550
Hospitalization (days)	3.114±0.404	3.086±0.284	0.733

Hb: Hemoglobin, SD: Standard deviation

Table 3: Correlation between prostate size and blood loss

Pearson correlation coefficient	Intra operative blood loss®	*P*
Prostate size	0.550**	0.000
n	70	

**Correlation is significant at the 0.01 level (two-tailed)

Table 4: Sub group analysis in intra operative blood loss according to prostate size

Prostate size (g)	Groups	Number of patients	Blood loss (ml)	SD	*P*
20-40	Cases	6	66.95	20.22	0.036
	Controls	12	154.01	90.57	
41-60	Cases	14	163.8500	116.08	0.14
	Controls	14	218.62	72.40	
>60	Cases	15	227.69	131.97	0.019
	Controls	9	358.60	103.47	

SD: Standard deviation

also been used effectively as a topical agent for reducing blood loss in various procedures and in cases of gross hematuria.[7-11,14]

The results of this study showed a significant reduction in intraoperative bleeding with mean blood loss in the TXA group 174.6 ± 125.38 ml as compared to 232.47 ± 116.8 ml in the control group (P = 0.04). A meta-analysis and systematic review by Mina and Garcia-Perdomo[15] and Longo *et al*.[16] also confirmed the effectiveness of TXA in reducing perioperative blood loss. This would mean TXA could decrease intraoperative trauma and transfusion risk.

In this study, transfusion was required in 5 out of 35 (14.2%) patients in the control group as opposed to just 1 (2.8%) patients requiring transfusion in TXA group. Similar rates of transfusion were found in a recent study by Jendoubi *et al*.[17] Even though this rate is higher than in literature, could be because of strict criteria followed for transfusion. This reduction in the need for transfusion is contrary to the recent meta-analysis by Mina and Garcia-Perdomo.[15] In this study, this decrease in the need for blood transfusion maybe because of the use of TXA topically, increasing its local concentration, also simultaneously reducing the systemic side effects.

In this study, fall in hemoglobin concentration at 24 h of TURP was found to be 1.31 g/dl in the TXA group and 1.4 g/dl in the control group. Even though this does mean an absolute decrease in hemoglobin, was not found to be significant (P = 0.722). In a study including 40 subjects by Kumsar *et al*., in which 10 mg/kg TXA was administered 30 min before surgery absolute difference in the decrease of hemoglobin between the groups was 0.27 mg/dl, which was not significant.[13] In a systematic review of various studies by Longo *et al*., no significance was found in decreased hemoglobin concentration at 24 h post TURP even though intraoperative blood loss showed a significant reduction between the groups. It was thereby inferred that intraoperative blood loss as detected by spectrophotometric method may not correlate to 24-h postoperative hemoglobin concentration.[16]

In a study by Rannikko *et al*., 136 patients who underwent TURP surgery were administered 2 g IV TXA or placebo randomly; it was observed that 50% of patients in TXA group showed reduced intraoperative bleeding, which also translated to decreased operative time and reduced amount of irrigation fluid needed. This could also decrease the possibility of water absorption and TUR syndrome.[18] These findings were also observed in Kumsar *et al*.[13] In this study, however no significant difference was found between the two groups with respect to irrigation fluid volume (14.9 L vs. 15.5 L; P = 0.703) and operative time (56.71 min vs. 54.5 min; P = 0.55). Meng *et al*. in their study on 60 patients, did not find any significant difference in irrigation volumes and operative times between the groups.[19] The frequency of transurethral resection syndrome varies 0.18%–10.9%; therefore, a much larger pool of patients is needed to detect any statistically significant differences.[13] Therefore, it cannot be concluded with certainty as the study is conducted in a small number of patients.

In the current study, we also found the prostate size to be an independent risk factor for increased bleeding. This is also established in the current literature.[20] In subgroup analysis, it was found that blood was significantly reduced in larger prostate sizes (>60 g) when TXA was given (P = 0.019).

One of the major concerns with the use of TXA in patients undergoing TURP is the risk of thromboembolic events (TE). Several studies have demonstrated that TXA does not increase TE.[6,21,22] There is no single recommended dose or mode of delivery when applied in various procedures. However, compared to younger patients, elderly patients are at a higher risk of thrombosis, especially in lithotomy position as they are less active and blood viscosities are higher.[23] Thus for prostate surgery, the manufacturer suggests reducing the drug dosage in elderly patients. In this study, we combined the mode of delivery (intravenous as well as topical) to deliver an appropriate dose simultaneously decreasing the serum concentration of TXA levels as absorption when used locally is far less, which could also decrease the possibility of such events maintaining its effectiveness.

CONCLUSION

In this study, we observed that TXA effectively reduced intraoperative blood loss and need for transfusion. We also observed that its combined use by intravenous and topical route is very effective in reducing intraoperative blood loss, which comes at a very reasonable cost and wide margin of safety, especially in larger prostates.

Limitations

One of the major limitations in the study is the small sample size, which may lead to skewed results. The second limitation of this study was that the TURP procedure was done based on surgeon's preference and a single technique was not followed in all. Third, this study was performed by a group of expert surgeons and not a single surgeon. Finally, resected prostatic tissue was not weighed and prostate size was solely relied based on ultrasound only.

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Conflicts of interest

There are no conflicts of interest.

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