EGYPTIAN JOURNAL OF ANAESTHESIA
2022, VOL. 38, NO. 1, 491–496
https://doi.org/10.1080/11101849.2022.2113703

Evaluation of efficacy and safety of intraoperative tranexamic acid: prospective placebo-controlled comparative study

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ABSTRACT

Objectives: Evaluation of the effect and safety of intravenous and local application of tranexamic acid (TXA) on outcomes of transurethral resection of the prostate (TURP).

Patients & Methods: 138 patients were divided into three groups according to the mode of TXA delivery (Groups I and II) or placebo. Hemoglobin concentration (HBC) and hematocrit value (HTC) were determined before and immediately after surgery to calculate hemoglobin deficit and estimated intraoperative blood loss (IO-BL). All surgeries were performed under bupivacaine spinal anesthesia with the preoperative saline co-load infusion.

Results: Patients who received: combined IV and local delivery of TXA showed significantly shorter operative time and duration of PO catheterization and hospital stay than patients of other groups. The IO-BL was significantly lower in patients received TXA than placebo. Hemoglobin deficit after surgery was significantly lower in patients received both IV and local delivery of TXA than patients of other groups. No adverse effects of TXA s were reported.

Conclusion: The applied policy for antifibrinolysis during TURP was safe and effectively improved operative and immediate PO outcomes.

ARTICLE HISTORY
Received 18 May 2022
Revised 8 August 2022
Accepted 11 August 2022

KEYWORDS
Tranexamic acid; intravenous infusion; irrigation fluid; hemoglobin deficit; intraoperative blood loss

1. Introduction

Tranexamic acid, which is a synthetic analog of the amino acid lysine, competitively inhibits the formation of the fibrinolysis complex through binding to lysine binding sites on plasminogen [1] to prevent its activation to plasmin with subsequent prevention of fibrinolysis and stabilization of the fibrin-rich clot [2]. TXA was on the list of World Health Organization essential medicines that are used to treat severe bleeding events for nearly 60 years [3]. TXA is used to control both intraoperative (IO) and postoperative (PO) bleeding during various surgical procedures [4]. Moreover, TXA was found to indirectly reduce post-surgery infection rates [5] and to decrease hemorrhage-related mortality in trauma patients [4].

TXA is routinely given intravenously, however, oral administration and local delivery of TXA to bleeding sites were found to achieve an effective and prolonged anti-fibrinolytic effect during various orthopedic surgeries [6,7]. Moreover, local delivery was found to be as effective as an intravenous infusion [8].

Transurethral resection of the prostate (TURP) is still the "gold standard" surgical treatment for medication-refractory benign prostatic hyperplasia (BPH) [9], but the incidence of IO and PO complications accounts for about 15% with bleeding is the most frequent complication [10].

1.1. Objectives

This study targets to evaluate the effect and safety of the intravenous and local delivery of TXA during TURP.

1.2. Design

Prospective interventional multicenter placebo-controlled comparative study.

1.3. Setting

Departments of Anesthesia, Faculty of Medicine, Tanta and Cairo Universities, and multiple private urology centers at Cairo and Tanta.

1.4. Ethical consideration

The study protocol was approved by the Local Ethical Committee at Tanta Faculty of Medicine (Approval code: 35,461/4/22). For blindness purposes, the authors and surgeons were blinded during the preparation of the wash fluid.

1.5. Sample size calculation

According to the published results obtained by Abboud et al. [11] regarding the effect of using combined intravenous and topical tranexamic acid in

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reduction of perioperative and considering the null hypothesis was as the absence of difference between all groups with a delta of 0.07, moderate effect size of 0.25 among 3 groups, using estimated sample sizes for one way ANOVA F test, the required minimal sample size was 42 subjects per group for a total sample size of 126 subjects to achieve a study power of 80% with α error of 5%. For possible attrition, sample size was increased to 138. Sample size was calculated by the STATA software (Stata Corp, 2021, Version 17).

1.6. Patients & methods

All patients assigned to TURP for BPH were evaluated for exclusion and inclusion criteria.

1.7. Exclusion criteria

Patients with coagulopathy, renal, liver, or cardiac diseases, obesity of grade II with body mass index (BMI) >35 kg/m^2, allergy to the study drugs, maintenance on drug therapy that may interact with TXA, presence of other prostatic or urinary bladder pathologies, refusal to receive neuraxial anesthesia or to sign the written consent were excluded from the study.

1.8. Inclusion criteria

Patients presenting with manifestations of obstructive uropathy secondary to BPH and were free of exclusion criteria were enrolled in the study.

1.9. Preoperative evaluation

(1) Determination of demographic data including age, weight, and height to calculate the BMI according to the equation: BMI = weight (kg)/ height (m^2).
(2) Clinical examination includes the estimation of baseline hemodynamic data, ECG, and evaluation of the vertebral column for any deformity or obstacle to insertion of the spinal needle.
(3) Laboratory investigations include the determination of hemoglobin concentration (HGC), hematocrit value (Hct value), complete blood count, serum urea and creatinine, clotting, and bleeding times.

1.10. Randomization and grouping

Randomization sequence was created using Excel 2007 (Microsoft, Redmond, WA, USA) with a 1:1 allocation using random block sizes of 2 and 4 by an independent doctor. In this way, sequence generation and type of randomization can be expressed at the same time. For blindness purposes, the generated sequences were transformed as cards carrying group labels (I, II, III) put in sealed envelopes and was given to patient to provide it to the anesthetist, not the author, who was responsible for the preparation of the study infusions and irrigation fluids.

1.11. Preparation of infusions and irrigation fluids

(1) Intravenous infusions: three saline (0.9% NaCl) bottles were prepared and labeled I which is plain saline and II and III which contain TXA (Kapron, 500 mg/ 5 ml amp, Amoun Pharmaceuticals, Egypt) infusion of 500 mg/500 ml saline to provide 1:1 (wt: vol). Dose of TXA infusion was adjusted according to guidelines of the PeriOpeRative Tranexamic acid in hip arthrOplasty (PORTO) study investigators who used a preoperative IV bolus of TXA 1 g followed by a continuous infusion of either TXA 1 g or placebo over 8 h [12]. IV infusions were started preoperatively at the time of induction of anesthesia till end of surgery and then were stopped.
(2) Irrigation fluid: normal saline (0.9 NaCl) was used as irrigation fluid; for patients of groups I and II saline irrigation bottles were free of TXA, while for patients of group III saline was mixed with TXA to provide 1 mg TXA for each 6 ml saline to provide 1:6 (wt: vol).

1.12. Anesthetic procedure

On arrival at the pre-anesthetic room, an 18-gauze cannula was inserted under complete aseptic conditions to prepare IV access and all patients were co-loaded with normal saline at a rate of 6 ml/kg/hr. Standard monitors were applied for non-invasive monitoring of heart rate, blood pressure, electrocardiography, and oxygen saturation. Central venous line, which is invasive procedure was not applied because the irrigation fluid to be used was saline not glycine, so there was no chance for hypervolemia. In the operating room, patients were kept in a set position, and after sterilization of the back, a 22-gauze needle was inserted at the level of L_{3-4} or L_{4-5} intervertebral space via midline or paramedian approach and 3-ml of 0.5% bupivacaine were injected after ensuring free flow of cerebrospinal fluid. Then, patients were placed in a supine position with one pillow. Non-invasive monitoring of hemodynamic variables was performed every 5-min all through operative time. Hypotension was considered if the mean arterial measure dropped by >20% of baseline value and was managed by intravenous injection of phenylephrine as a 50 µg bolus dose that was repeated after 5 min if indicated. Bradycardia was managed with intravenous atropine injection in a dose of 0.6 mg if the heart rate was dropped to <60/min. Surgeries were performed with

a Storz 24 Fr resectoscope, by one team in each institute. After completion of resection, a 20 Fr 3-way urethral Foley catheter with compression catheter balloon was applied to minimize the blood loss in all cases and bladder irrigation was stopped, so calculation of the postoperative blood loss was neglected as it will not be related to the study drug. Continuous normal saline irrigation was started after release of compression balloon until the urine drained from the urethral catheter became clear in the absence of irrigation and then catheters were removed and patients were discharged upon spontaneous voiding.

1.13. Evaluation of efficacy of anti-fibrinolytic therapy

- Estimated intraoperative blood loss (IO-BL) was calculated using the Gross formula [13] where BL = BV [HCT (i) – HCT (f)], where BV (ml) is the calculated blood volume as body weight (kg) multiplied by 70 [14], HCT (i) and HCT (f) were the initial (preoperative) and final (postoperative) hematocrit values, respectively.
- Hemoglobin deficit was calculated as the difference between preoperative and immediate PO hemoglobin concentration (HBC).
- The frequency of blood transfusion and the number of transfused blood units were also determined, if required.

1.14. Study outcomes

(1) The efficacy of anti-fibrinolytic therapy used for patients of groups II and III in comparison to group I
(2) The efficacy of the use of combined IV and local delivery of anti-fibrinolytic therapy compared to IV therapy only.
(3) The frequency of PO complications

2. Statistical methods

Data are presented as mean, standard deviation, median, interquartile range, numbers and percentages. Student t-test was used to determine the statistical significance of the difference between the mean values of two study group. One-way analysis of variance (ANOVA) was used for the comparison between mean values of more than two groups and Post-hoc test was followed to determine the difference between mean values of multiple groups. Mann Whitney Test (U test) was used to assess the statistical significance of the difference in non-parametric variables between two study groups. Chi-Square test was used to examine the relationship between two qualitative variables. Statistical analysis was conducted using IBM® SPSS® Statistics (Version 25, 2017; IBM Corp, Armonk, NY, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

3. Results

During the study duration, 167 patients were eligible for evaluation; 29 were excluded for not fulfilling the inclusion criteria and 138 patients were randomly allocated into the three groups (Figure 1). The enrolment demographic and clinical data showed non-significant differences between patients of the three groups as shown in Table 1.

The weight of the resected prostatic tissue and the used volume of irrigation fluid showed a non-significant inter-group difference. The median value of intravenous dose used through intraoperative infusion was non-significant between patients of groups II and III. Operative time, duration of PO catheterization and hospital stay were significantly shorter in patients of group III compared to patients of group I and II with non-significant differences between patients of groups I and II (Table 2).

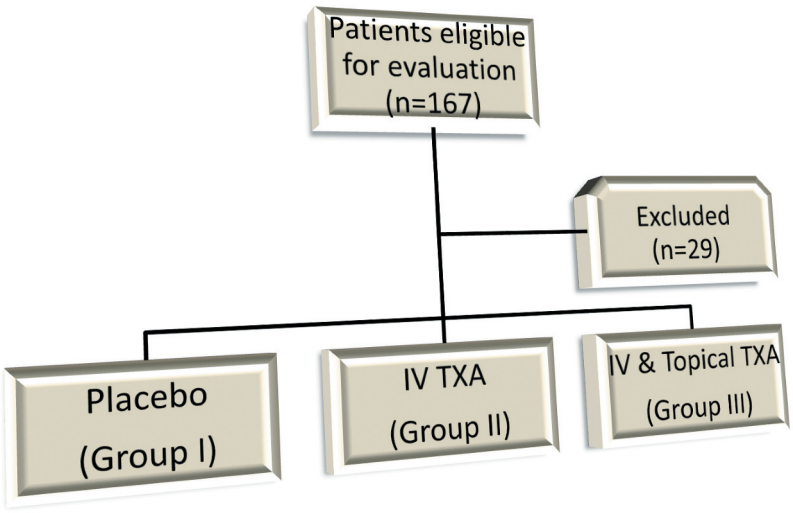

Figure 1. Study flowchart.

Table 1. Patients' enrolment data.

Variables	Group I	Group II	Group III	P1	P2	P3
Age (years)	66.3 ± 4.15	66.5 ± 3.9	66.8 ± 5.3	0.976	0.855	0.944
Weight (kg)	89 ± 5.2	88 ± 5.7	88.5 ± 5.4	0.656	0.899	0.899
Height (cm)	171 ± 4.8	170.5 ± 3.4	169 ± 3.8	0.826	0.052	0.185
BMI (kg/m^2)	30.2 ± 2.14	30.3 ± 2.4	31 ± 2.1	0.977	0.207	0.295
US-estimated PV(cc)	65 ± 7.6	67 ± 5	67.9 ± 5.5	0.262	0.064	0.764

Data are presented as a mean and standard deviation; IV TXA: Intravenous tranexamic; BMI: Body mass index; US: Ultrasound; PV: Prostatic volume; P1 value indicates the significance of the difference between groups I &II; P2 value indicates the significance of the difference between groups I &III; P3 value indicates the significance of the difference between groups II & III; $P < 0.05$ indicates a significant difference; $P > 0.05$ indicates a non-significant difference

Table 2. Operative and immediate PO data.

Variables		Group I	Group II	Group III	P1	P2	P3
Weight of the resected prostatic tissue (gm.)		17.7 ± 1.85	17.2 ± 1.6	17.5 ± 1.9	0.378	0.855	0.703
Operative time (min)		49.2 ± 5.3	47.7 ± 5.7	46.4 ± 6	0.241	0.024	0.136
Number of bottles used for IO irrigation*		6 [5.5–6.5]	5.5 [5–6.5]	5.55 [5–6.1]	0.242	0.053	0.352
Dose of TXA(mg/ kg BW)*	IV infusion	0	7.5 [7.3–7.8]	7.4 [7.3–7.9]	0	0	0.659
	Irrigation fluid	0	0	40.7 [36–47]	0	0	0
	Total dose	0	7.5 [7.3–7.8]	48 [43.5–54.8]	0	0	0
Catheter duration (hrs.)		93.9 ± 32.2	91.7 ± 29.7	77.1 ± 21.3	0.927	0.013	0.037
Hospital stay (days)		4.1 ± 1.4	4 ± 1.3	3.3 ± 0.9	0.662	0.004	0.002

Data are presented as mean and standard deviation, median and interquartile range [IQR]*; TXA: Tranexamic acid; BW: Bodyweight; P1 value indicates the significance of the difference between groups I & II; P2 value indicates the significance of the difference between groups I & III; P3 value indicates the significance of the difference between groups II & III; $P < 0.05$ indicates a significant difference; $P > 0.05$ indicates a non-significant difference

Preoperative HTC-i and HBC-i showed non-significant differences between studied groups, but were significantly higher than PO values (HTC-f and HBC-f). However, the HTC-f value of patients of group I was significantly lower in comparison to that of patients of group II ($p = 0.0084$) and group III ($p = 0.0009$) with a non-significantly ($p = 0.774$) higher HTC-f value of patients of group III in comparison to patients of group II.

The estimated IO-BL loss was significantly lower in patients of group III compared to patients of groups I ($p < 0.001$) and II ($p = 0.0044$) with significantly ($p < 0.001$) lower IO-BL in patients of group II than patients of group I. On contrary, HBC-f of patients of group III was significantly ($p = 0.0019$) higher but was non-significantly ($p = 0.203$) higher compared to patients of groups I and II, respectively with non-significantly ($p = 0.181$) higher HBC-f value in patients of group II. However, HBC deficit was significantly ($p < 0.001$) lower in patients of group III compared to patients of other with significantly ($p = 0.0006$) lower HBC deficit in patients of group II than group I. Only one patient in group I required transfusion of one bag of blood to correct his PO hemoglobin concentration (Table 3).

4. Discussion

The preoperative use of TXA significantly minimized intraoperative (IO) bleeding compared to placebo; this finding goes in hand with the recently documented as regarding the advantageous use of TXA for control of IO bleeding, irrespective of the type of surgery [15,16] and could be attributed to its mechanism of action through blockage of plasminogen-lysine binding sites to prevent binding of fibrin with subsequent stabilization of fibrin clot and prevention of bleeding [17–19]. Moreover, preoperative injection of a loading dose with induction of anesthesia before inflection of tissue injury and continuation with intravenous infusion during surgery, which continued for less than 60 min, could be a piece of practical evidence for the efficacy of the applied policy of the combined use of antifibrinolytic drugs as prophylaxis and therapy during surgery for control of perioperative bleeding and supported the previous work used similar policy during orthopedic surgeries [20–22].

Application of the antifibrinolytic drug direct topically through the irrigation fluid significantly reduced the amount of blood in the returning fluid in patients who received intravenous and local antifibrinolytic drug compared to patients who received intravenous injection only. The obtained superior outcome was reflected as shorter operative and PO hospital stay times and spared the needs for transfusion without increasing the thromboembolic risks as previously documented [7,23–27].

Using a similar combination in a placebo controlled study, Gupta et al. [28] detected significant reduction of bleeding and need for transfusion, but reported non-significant differences in PO HBC and did not explain this discrepancy. On contrary, the present work reported a significantly lower HBC deficit with the used combination compared to IV TXA only or placebo. Moreover, Gupta et al. [28] used intravenous drug 500 mg as a shot dose and 500 mg/3-L bottles for a maximum topical dose of 1.5 g of TXA; 3 bottles for a total dose of 2 g/patient. However, the mean number of bottles they were used was 5 (±1.5), thus there were plain two bottles (6 liters) were used without any

Table 3. Hematological data at end of surgery in comparison to preoperative data of patients of the three study groups.

Variables	Group	I	II	III	P1	P2	P3
Estimated IO-BL	HTC-i (%)	39.5 ± 1.95	39.4 ± 2.1	39.2 ± 2.4	0.979	0.833	0.922
	HTC-f (%)	36.1 ± 1.65	37.5 ± 2.2	37.8 ± 2.5	0.0084	0.0009	0.774
	P4 value	<0.001	<0.001	0.006			
	EBL (ml)	548.5 ± 142	307.8 ± 95	233 ± 87.6	<0.001	<0.001	0.0044
Calculated HB deficit	HBC-i (g/dl)	12.8 ± 0.9	12.9 ± 1	12.8 ± 0.9	0.816	0.987	0.892
	HBC-f (g/dl)	11.5 ± 0.8	11.8 ± 1	12.1 ± 0.9	0.181	0.0019	0.203
	P4 value	<0.001	<0.001	0.0004			
	Deficit (%)	10 [9.1–11.15]	8.58 [7.3–10.2]	5.44 [4.3–6.4]	0.0006	<0.001	<0.001

Data are presented as mean and standard deviation, median and interquartile range [IQR]; HTC-i: preoperative hematocrit; HTC-f: Hematocrit value estimated at end of surgery; HBC-i: preoperative hemoglobin concentration; HBC-f: Hemoglobin concentration estimated at end of surgery; EBL: Estimated blood loss; HB: Hemoglobin; P1 value indicates the significance of the difference between groups I &II; P2 value indicates the significance of the difference between groups I & III; P3 value indicates the significance of the difference between groups II & III; P4 value indicates the significance of the difference between estimations at the end of surgery and preoperatively; $P < 0.05$ indicates a significant difference; $P > 0.05$ indicates a non-significant difference

explanation. In line with the obtained results, a recently published study assured the efficacy and safety of the use of TXA in the irrigation fluid during TURP [29].

The calculated median of the total dose of used in the current study was about 48 mg/kg body weight for each of patients who received combined route therapy and considering the mean weight was 88 kg, so the median total dose was about 4 g of TXA and no adverse effects were reported. In line with the efficacy and safety of this dose, Jansen et al. [8] compared combined IV, oral and topical TXA in three doses; ≤10 mg/kg, >10-25 mg/kg and >25-50 mg/kg for patients had previous thromboembolic events within 12 months ago and undergoing total knee arthroplasty, and reported shorter hospital stay and smaller hemoglobin deficit with a dose of >25-50 mg/kg compared to ≤10 mg/kg and reported no difference in complication rates. Recently, Chen et al. [30] found IV TXA in a dose of ≥3 g/dl significantly reduced total blood loss and duration of hospital stay compared to 1 g/dl or 2 g/dl dose. Moreover, Poeran et al. [31] documented the effectiveness and safety of, irrespective of the patient's high-risk status at baseline. Thereafter, Wang et al. [32] compared the efficacy and safety of TXA at a dose of >50 mg/kg versus <50 mg/kg and found TXA dosage did not impact survival, thromboembolic events, or blood management.

Regarding the type and amount of irrigation fluid, the median number of bottles (500 ml each) was 6, 5.5 and 5.5 bottles for groups' I–III, respectively for a median total amount of saline used of 3000 ml (Table 2), which is in line with that previously used by Gupta et al. [28] and less than that used by recently published studies [33]. Moreover, complications related to irrigation fluid during TURP was documented for glycine irrigation fluid not for saline that if occurred it was documented as case report [34] and a recently published work reported an incidence of TURP syndrome of 4% after glycine irrigation [29].

5. Conclusion

Combined intravenous injection and topical TXA safely and effectively reduces bleeding and time of urinary bladder drainage and hospitalization of patients undergoing urethroscopic prostatic resection.

Acknowledgments

The authors provide great thanks to staff members of the Urology Departments at the hospitals included in the study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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