

Topical vs. intravenous administration of tranexamic acid to minimize blood loss in abdominal hysterectomy perioperatively: A randomized controlled study

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Abstract

Background and Aims: Topical application of tranexamic acid (TXA) to bleeding wound surfaces is rapidly gaining recognition and currently a topic of further research in patients undergoing abdominal hysterectomy. The aim of the study was to compare the efficacy of topical vs. intravenous (i.v.) administration of TXA in reducing perioperative blood loss in patients undergoing abdominal hysterectomy.

Material and Methods: A double-blinded parallel-group randomized controlled study was conducted in a tertiary teaching institute. Group 1 ($n = 25$) received 10 mg.kg⁻¹ i.v. bolus of TXA after induction followed by infusion of 1 mg.kg⁻¹.h⁻¹ of TXA, in 50 ml of normal saline (NS), till the completion of surgery and just before closure of peritoneum 100 ml of NS was applied topically over the raw surface. Group 2 ($n = 25$) received 50 ml of NS over 10 min after induction, followed by infusion of 50 ml of NS, till the completion of surgery and just before closure of peritoneum, 1.5 g of TXA mixed in 100 ml of NS was applied topically over the raw surface. The primary outcome was total perioperative blood loss (intraoperative plus 24 h postoperative). The secondary outcomes included change in hemoglobin concentration postoperatively at 12 h, 24 h; need for blood/blood product transfusion; amount of blood/blood product transfused and side effects of TXA.

Results: Total perioperative blood loss was 312 ± 106.65 ml in group 1 and 325 ± 89.90 ml in group 2 ($p = 0.659$). It was found that the mean reduction in hemoglobin was 0.7 g.dl⁻¹ and 0.54 g.dl⁻¹ in group 1 and 0.67 g.dl⁻¹ and 0.44 g.dl⁻¹ in group 2 at 12 h and 24 h respectively, with no significant intergroup difference.

Conclusion: Administration of TXA topically is as efficacious as TXA administered i.v. to minimize perioperative blood loss in patients undergoing abdominal hysterectomy.

Keywords: Hysterectomy, intravenous, randomized controlled, topical, tranexamic acid

Introduction

Hysterectomy is one of the most commonly performed major gynecological surgical procedures with blood loss as its most common intraoperative complication.^[1] The estimated blood loss during open abdominal radical hysterectomy is approximately 540 ml (range 80–3000 ml depending upon the cause for hysterectomy; oncological surgeries result in

higher blood loss. Even in oncologic setup it depends on stage of the disease, previous chemoradiation, etc.) with 15% requiring blood transfusions.^[2] Blood transfusion has its own complications; therefore, prevention of blood loss is quintessential. Tranexamic acid (TXA), an antifibrinolytic has been used in prevention of blood loss in cardiac surgery, trauma, liver surgery, neurosurgery, and obstetric hemorrhage.^[3]

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It is now established that intravenous (i.v.) TXA reduces surgical blood loss and need for blood transfusion.^[4] Further, topical administration of TXA as opposed to the usual i.v. route is rapidly gaining recognition and currently a topic of further research. This is because of the possible safety due to less systemic absorption while ensuring efficacy of the topical application.^[5] TXA has been used topically in total knee arthroplasty and was found to be a safe and effective method to reduce blood loss and RBC transfusion rates.^[6,7] However, there is scarce data available in literature on topical use of TXA in patients undergoing hysterectomy.^[8]

The aim of the study was to compare the efficacy of topical vs. i.v. administration of TXA in reducing perioperative blood loss in patients undergoing abdominal hysterectomy.

Material and Methods

This was a double-blinded, parallel-group, randomized controlled study (RCT). Approval for study was obtained from the Institute Ethics Committee [Ethics/2016/0002 dated 03.05.2016], and informed and written consent was obtained from each patient prior to enrollment in the study. The study was performed in accordance with the ethical standards of the institutional and/or national research committee and Declaration of Helsinki.

Fifty patients belonging to American Society of Anesthesiologists (ASA) physical grade I or II with age 35-70 years admitted to the Obstetrics and Gynecology department for abdominal hysterectomy were recruited prospectively from November 2015 to October 2016. Patients who were excluded from the study were: ASA physical status III or IV; Hb <8 g.dl⁻¹; allergy to TXA; emergency hysterectomy after cesarean delivery; refusal of blood products, e.g., Jehovah's witnesses; history of either epilepsy, thromboembolic events (acute coronary syndromes, cerebrovascular events or deep vein thrombosis) or eye problems (retinal involvement, acquired color blindness); patients with evidence of coagulopathy and those on low dose aspirin or other antiplatelet or anticoagulant drug like warfarin. All the enrolled patients were evaluated preoperatively on the day prior to the surgery. General, physical and systemic examination was conducted to assess the fitness for the proposed surgical procedure under general anesthesia. Written informed consent was obtained from all the patients. Preoperatively, hemoglobin concentration, hematocrit, platelet count, prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT) were measured on the day before operation.

After confirming nil per oral status, the patients were taken to the operation theater. In the operation theater, i.v. line was secured and standard ASA monitors were applied. Then, the patients were randomized using computer-generated random number table and allocated by coded sealed opaque envelopes to either Group 1 (i.v. TXA) or Group 2 (topical TXA).

The drugs were prepared by an anesthesiologist not involved in the collection and analysis of data. The precise calculated dose of the drug (TXA) according to body weight was prepared in identical looking 50 ml syringes, diluted to a total volume of 50 ml in Group 1. To maintain blinding, normal saline (NS) was also drawn in identical looking 50 ml syringes in Group 2.

Similarly, under all aseptic conditions, TXA (1.5 g mixed in 100 ml of NS) and NS for topical application over the raw surgical surface in Groups 1 and 2 were also prepared, respectively.

In both the groups, standard general anesthesia technique was followed, using morphine 0.1 mg.kg⁻¹ and propofol 2.0 mg.kg⁻¹ intravenously for induction and vecuronium 0.1 mg.kg⁻¹ intravenously for neuromuscular blockade. The tracheal intubation was done and maintained on controlled ventilation with 60% N₂O: 40% O₂ with 0.6%–1.0% isoflurane.

Group 1 (i.v. TXA, *n* = 25) received bolus of 10 mg.kg⁻¹ of TXA in 50 ml of NS i.v. over 10 min after induction followed by a maintenance infusion of 1 mg.kg⁻¹.h⁻¹ of TXA, in 50 ml of NS. Just before closure of peritoneum, 100 ml of NS was applied topically over the raw surface.

Group 2 (topical TXA, *n* = 25) received bolus of 50 ml of NS, over 10 min after induction, followed by a maintenance infusion of 50 ml of NS. Just before closure of peritoneum, 1.5 g of TXA mixed in 100 ml of NS was applied topically over the raw surface.

In both the groups, the bolus and infusion were administered by the principal investigator using a Simtek Infutek 405 syringe infusion pump (Simtek Medico Systems Pvt. Ltd., Goregaon, Mumbai) till the completion of the surgery. The principal investigator was blinded to the study drug.

The patients were monitored for pulse, blood pressure, electrocardiogram and end-tidal carbon dioxide during the surgery. Neuromuscular blockade was reversed with neostigmine and glycopyrrolate at the end of the surgery.

Hemodynamic parameters (heart rate, systolic, diastolic and mean arterial blood pressure) were noted at regular

intervals, starting preoperatively till shifting the patients to postoperative area. NS was used as the replacement fluid for the estimated intraoperative blood volume lost in a 3:1 ratio. Patients received blood transfusion if total blood loss exceeded 20% of total blood volume or exceeded allowable blood loss.

Intraoperative blood loss was measured by adding the volume of blood in the suction bottles and the weight of sponges. Difference in weight of the sponge before and after use was converted to volume (ml) using density of blood as 1 gm/ml.^[9] Quantification of all the fluids added to the surgical field intraoperatively was done. They were deducted from the measured blood loss. Postoperative blood loss was measured from wound drainage of the surgical drain for the first 24 h postoperatively. Hemoglobin concentration, hemocrit, platelet count, PT/INR, and aPTT were measured on the day of operation at 12 and 24 h. Surgery was performed by the same surgeon. The surgeon was also blinded to the infusion of the study drug.

The number of units of packed red cells, pooled random donor platelets, and fresh frozen plasma transfused during the hospital stay were recorded. The patients were assessed for any thromboembolic event and complications like myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism daily till discharge and on follow-up at 2 weeks. Duration of surgery and total length of hospital stay were recorded.

The primary outcome measure was the total perioperative blood loss (ml) calculated as the sum of blood loss during intraoperative and 24 h postoperative period. The secondary outcome measures were change in hemoglobin concentration at 12 h and 24 h postoperatively, need for blood/blood product transfusion (hemoglobin level dropping to <7 g/dl); amount of blood/blood product transfused; side effects of TXA, including nausea-vomiting, blurry vision, perception of color change, and thromboembolic events (deep venous thrombosis, pulmonary embolism, myocardial infarction, and stroke). Since group allocation was concealed, decoding was done at the end of study.

Sample size calculation was done based on our hospital data. The average perioperative blood loss during hysterectomy for malignancy is 700 ml with a standard deviation of 300 ml (in round figures). Considering a hypothesized 40% reduction in blood loss with TXA in hysterectomy as in cesarean section^[10] the perioperative blood loss in the experimental group should be 400 ml (in round figures). Considering an alpha of 5% and power of 80%, the sample size for each group was calculated to be 20 each. Allowing for 25% oversampling

to accommodate patient or data attrition, it was decided to recruit 25 patients in each group (total sample size 50).

The statistical analysis was carried out using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA).^[11] Quantitative and qualitative variables were presented as mean \pm SD, median as appropriate and frequencies and percentages, respectively. Statistical testing for qualitative and quantitative data was done by Chi-square test and Student's *t*-test, respectively. $P < 0.05$ was considered statistically significant. Kaplan–Meier survival analysis was also carried out.

Results

A total of 64 patients were assessed for eligibility, out of which ten did not meet the inclusion criteria and four patients refused to participate in the study. The remaining 50 patients were randomly allocated to the two groups [Figure 1]. Both the groups were comparable in terms of demographic profile, indications for hysterectomy, and duration of surgery [Table 1]. There was no significant difference in hemodynamic parameters between the groups at various time points throughout the study period. Regarding the primary outcome of interest, it was found that the total perioperative blood loss (intraoperative and postoperative loss up to 24 h) was similar in the two groups (312 ± 106.65 ml in group 1 and 325 ± 89.90 ml in group 2) with P value of 0.659 [Table 2]. The mean reduction in hemoglobin was 0.76 ± 0.32 and 0.54 ± 0.32 g.dl⁻¹ at 12 and 24 h in group 1 and 0.67 ± 0.29 and 0.44 ± 0.35 g.dl⁻¹ at 12 and 24 h in group 2 with no significant intergroup difference ($p = 0.316$ and 0.181 , respectively) [Figure 2]. Eight patients in group 1 (32%) and five patients in group 2 (20%) required blood transfusion ($p = 0.33$) [Table 3].

There was no significant intergroup difference with regard to platelet count, coagulation profile (PTI/INR and APTT), and length of stay [Table 3]. None of the patients in both the groups had any gastrointestinal symptoms, blurring of vision, neurologic, or thromboembolic complication and mortality postoperatively till 2 weeks.

There was no difference in survival rates of both the groups using Kaplan–Meier analysis and log rank test (p value = 1.0).

Discussion

In this double-blind RCT, topical TXA was shown to have similar efficacy to i.v. TXA in reducing blood loss and

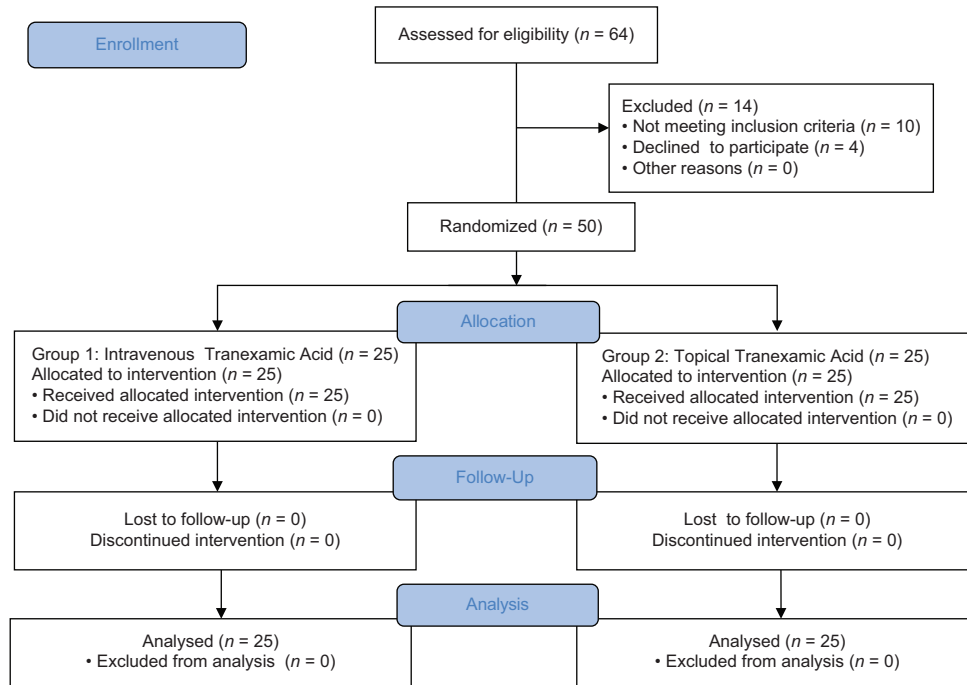


Figure 1: CONSORT flow diagram

Table 1: Demographic and clinical characteristics of patients undergoing abdominal hysterectomy receiving intravenous (i.v.) or topical tranexamic acid

Sample characteristics	Group 1 (IV TXA) [n=25]	Group 2 (topical TXA) [n=25]	P
Age in years (mean±SD)	46±10	48±9	0.986
Indication for hysterectomy n (%)			0.765
Fibroid	5 (20%)	5 (20%)	
Malignancy	4 (16%)	6 (24%)	
DUB	16 (64%)	14 (56%)	
Duration of surgery (hrs)[mean±SD]	2.17±0.26	1.91±0.43	0.135

i.v.: Intravenous; TXA: Tranexamic acid; DUB: Dysfunctional uterine bleeding

Table 2: Blood loss in patients receiving topical or intravenous (i.v.) tranexamic acid (TXA)

Blood loss	Group 1 (i.v. TXA) [n=25]	Group 2 (Topical TXA) [n=25]	P
Intraoperative blood loss ml±SD	246.4±95.52	259.2±82.65	0.614
24 h postoperative blood loss ml±SD	66.4±25.8	66±14.5	0.946
Total perioperative blood loss ml±SD	312±106.65	325±89.90	0.659

Values are in mean±standard deviation (SD)

transfusion requirements in patients undergoing abdominal hysterectomy, with similar adverse effects.

Perioperative TXA has been successfully used in various surgeries to reduce blood loss and the need for blood transfusion.^[12,13] The various modes of administration for TXA are, i.v., topical, oral, or a combination of any of these methods.^[14-16] i.v. application is frequently used, with evidence favoring its effectiveness in reducing blood loss and transfusion requirement in patients undergoing arthroplasty.^[14]

In major orthopedic surgeries the i.v. administration of TXA has been shown to reduce blood transfusion rates by

more than 60%.^[17] TXA as an i.v. agent has been widely studied in obstetric patients for postpartum hemorrhage and in cesarean section^[18-20] with efficacy in preventing blood loss.^[18-20] Very few studies were found in literature regarding use of prophylactic TXA in reducing the mean blood loss during gynecological procedures.^[9,21,22] Topsoe *et al.* and Caglar *et al.* demonstrated significant reduction in overall total blood loss with use of i.v. TXA in patients undergoing hysterectomy ($p = 0.004$) and myomectomy ($p = 0.03$), respectively.^[21,22]

However, adverse events have been reported with i.v. administration of TXA. They are dose-related acute

Table 3: Comparison of the secondary outcomes in both the groups

Secondary outcomes	Group 1 (IV TXA) [n=25]	Group 2 (Topical TXA) [n=25]	P
Preoperative			
Hb (g/dl)	11.38±1.12	10.94±1.20	0.199
Hematocrit (%)	34.14±3.41	32.84±3.63	0.199
PC (thousand mm ³)	220 (50)	210 (63)	0.293
PTI (s)	14.4±0.80	14±0.83	0.08
INR	1.04±0.074	1.07±0.061	0.122
APTT (s)	30.16±0.55	31.46±0.95	0.990
12 h Postoperative			
Hb (g/dl)	10.68±1.01	10.27±1.08	0.175
Hematocrit (%)	31.64±3.15	30.81±3.25	0.367
PC (thousand mm ³)	210 (53)	200 (49)	0.117
PTI (s)	14.8±0.99	14.36±0.77	0.08
INR	1.08±0.09	1.05±0.08	0.164
APTT (s)	31.08±1.52	30.64±1.25	0.185
24 h Postoperative			
Hb (g/dl)	10.84±0.90	10.5±0.96	0.199
Hematocrit (%)	32.53±2.72	31.5±2.90	0.200
PC (thousand mm ³)	212 (45)	200 (38)	0.09
PTI (s)	14.6±0.85	14.24±0.73	0.104
INR	1.06±0.080	1.03±0.069	0.164
APTT (s)	33.05±1.32	31.64±1.45	0.223
Blood transfusion (BT)			
No. of patients needing BT	8 (32%)	5 (20%)	0.332
Amount of BT* (ml)	250±92.58	320±178.88	0.687
Duration			
Length of stay (days)	4.32±0.85	4.62±1.2	0.352

Hb – Hemoglobin, PC - Platelet count, PT - Prothrombin time, INR - International normalized ratio, APTT- Activated partial thromboplastin time. *Blood was transfused using standard blood containing bags. In our hospital one unit contains 200 ml of packed red blood cells. Values are mean (SD), median (IQR [range]), and number (proportion)

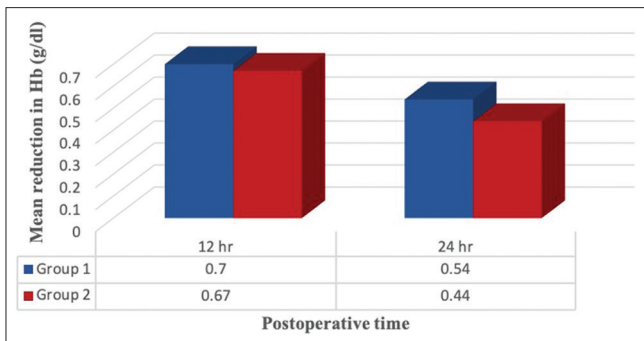


Figure 2: Figure showing mean reduction of hemoglobin (g/dl) in both the groups

gastrointestinal disturbances (nausea, vomiting, and diarrhea), prolonged use related visual disturbances (blurry vision and changes in color perception), and occasional thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, generally observed in the setting of active intravascular clotting such as thrombotic disseminated intravascular coagulation).^[23]

Many side effects mentioned above may preclude the use of i.v. TXA during surgery. Therefore, topical administration of TXA is gaining popularity in view of decreased side effects and systemic absorption. The topical use of TXA has also been found to

reduce perioperative blood loss in orthopedic replacement surgeries^[24-26] and cardiac surgeries.^[27] A recently published meta-analysis of 67 studies on topical TXA concluded with the recommendation that “further study of the topical application is required outside of the field of orthopedics.”^[28] There was none in gynecology. Our study is a step in that direction.

Therefore, in our study we compared the efficacy of topical TXA with i.v. TXA in patients undergoing abdominal hysterectomy in terms of minimizing the perioperative blood loss. We found that the total perioperative blood loss was comparable ($p = 0.659$) with no significant difference observed in mean hemoglobin drop measured at 12 and 24 h postoperatively ($p = 0.316, 0.181$) in both the groups [Table 2 and Figure 2]. Though nonsignificant, topical group reduced transfusion rates similar to i.v. group (p value = 0.33). No patient had any side effects in both the groups. Thus, topical TXA has similar efficacy to i.v. TXA in reducing blood loss and transfusion requirements.

Our results are comparable to the only recently published study comparing i.v. with topical TXA in patients undergoing hysterectomy. Sallam and Shady demonstrated

that there was no significant difference between the two groups (i.v. and topical TXA) (401.74 ± 121.67 ml and 395.35 ± 117.61 ml; $P = 0.804$) in minimizing perioperative blood loss, whereas both the groups were more effective than a saline-only control group (609.19 ± 119.14 ml; $P = 0.0001$) in reducing blood loss. In the i.v. group, 14% patients and in the topical group, 16.3% patients had blood loss more than 500 ml ($p = 0.763$) These results are similar to those in our study in terms of hemoglobin change ($p = 0.832$), requirement for blood transfusions ($p = 0.499$), side effects of TXA ($p > 0.05$), and duration of hospital stay ($p = 0.174$).^[8] These similarities in the two studies are important in view of the fact that there are differences in administration of topical and i.v. TXA in terms of timing and dosage from our study. Sallam and Shady used 2 g of TXA in topical group perioperatively, with 1 g diluted in 50 ml of NS (60 ml) irrigated in surgical field throughout the surgery and the remaining 1 g TXA diluted in 50 ml of NS (60 ml) administered topically at the end of the surgery. In their i.v. group, patients received 1 g TXA in 100 ml NS slowly infused at the rate of 1 ml per min.^[8] Thus, despite using a lower topical dose of TXA in our study (1.5 vs. 2 g in Sallam and Shady^[8]), the similar results boost the confidence and the generalizability of the findings.

Our results also show good congruence with recently published meta-analysis by Wang *et al.*^[24] and Montroy *et al.*^[28] They also reported there was no statistically significant difference in blood loss, transfusion requirement, and thromboembolic complications when comparing topical TXA and i.v. TXA in patients undergoing primary total knee replacement surgery^[24-26] and orthopedic and cardiopulmonary surgeries,^[28] respectively.

Our results are also comparable to Bondok *et al.*^[29] They also reported significant reduction in blood loss and transfusion requirements with lesser time taken to perform upper gastrointestinal endoscopy in patients who received TXA via nasogastric tube in patients with liver cirrhosis.^[29]

The possible mechanism and advantage of topical use of TXA into the surgical field is to directly target the site of bleeding just before wound closure, but after achieving hemostasis, thus attenuating the marked increase in local fibrinolysis. Such inhibited local fibrinolytic activity will help to prevent fibrin clot dissolution and increase its volume and strength at the surgical surfaces, and therefore, enhance microvascular hemostasis.^[30]

The present study had a few limitations. Our study might be underpowered for detecting the side effects of TXA as

no significant difference was found in side effects of TXA use, such as deep vein thrombosis and pulmonary embolism. Moreover, D-dimer was also not done in all the patients. Because no previous study was available at commencement of our study, efficacy of TXA in minimizing blood loss in cesarean section was used for calculating sample size.

To conclude, administration of TXA topically is as efficacious as TXA administered i.v. to minimize perioperative blood loss in patients undergoing abdominal hysterectomy. Therefore, topical TXA could be widely adopted in patients undergoing hysterectomy to reduce perioperative blood loss eliminating the side effects of i.v. TXA.

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Conflicts of interest

There are no conflicts of interest.

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