Single intravenous bolus versus perioperative continuous infusion of tranexamic acid to reduce blood loss in abdominal oncosurgical procedures: A prospective randomized double-blind clinical study

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Abstract

Background and Aims: Intraoperative use of a single bolus dose of tranexamic acid may not be sufficient to prevent bleeding in the early postoperative period. The present study was carried out to compare the effect of two dose regimens of tranexamic acid in reducing perioperative blood loss and the amount of allogenic blood transfusion in abdominal tumor surgery.

Material and Methods: In this prospective, controlled, and double-blind investigation, 60 patients electively posted for abdominal oncosurgical procedures were randomly assigned to receive a single bolus dose of tranexamic acid (10 mg/kg) (Group A), a bolus dose of tranexamic acid (10 mg/kg) followed by infusion (1 mg/kg/h) till 4 h postoperatively (Group B), and a bolus followed by infusion of normal saline (group C). Total intraoperative blood loss, amount of allogenic blood transfusion, postoperative drain collections, and hemoglobin and hematocrit levels were recorded at different time intervals. Data obtained after comparing three groups were analyzed by analysis of variance test for variables following normal distribution, Kruskal–Wallis test for nonparametric data, and post-hoc Tukey–Kramer test for intergroup analysis. A probability value of less than 5% was considered significant.

Results: There was no significant difference in intraoperative blood loss in all the three groups. Both the tranexamic acid groups showed reduction in postoperative blood collection in drain at 6 h and 24 h in comparison to the control group ($P < 0.001$). There was also a significant difference in the amount of blood in postoperative drain at 24 h within the tranexamic acid groups, where lesser collection was seen in the infusion group ($P = 0.007$). Hemoglobin and hematocrit levels measured at different postoperative time intervals showed a significant reduction from the baseline in the control group compared to the tranexamic acid groups together.

Conclusion: Tranexamic acid causes more effective reduction in post-operative blood loss when used as a bolus followed by an infusion continued in the postoperative period in comparison to its use as a single intravenous bolus in abdominal tumor surgery.

Keywords: Antifibrinolytics, blood loss, cancer, tranexamic acid

Introduction

Maintaining hemostasis in abdominal oncosurgery is a challenge because of unusual long duration of surgical procedures, significant fluid and blood loss, poor nutritional condition secondary to the cancer pathophysiology, grade of the tumor, cancer-related anemia, and fibrous adhesions following previous surgeries and radiotherapy.[1] Decrease in hemoglobin following blood loss is associated with a poor

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surgical outcome, delayed postoperative ambulation, and increased morbidity.[2]

Abdominal tumor surgeries are known to be associated with excessive blood loss. For example, myomatous uteri have an increased vascularity leading to significant blood loss during myomectomy. Similarly, cytoreductive surgery in advanced ovarian carcinoma with extensive intraperitoneal metastasis stands a high risk of bleeding.[3,4] Such surgeries carry an increased risk of postoperative anemia and postoperative morbidity owing to blood loss, and therefore, demand appropriate measures for hemostasis.

Tranexamic acid has been extensively studied to reduce blood loss in orthopedic surgery,[5-8] spine surgery,[9-11] gynecological procedures,[12-14] and cardiac surgery.[15-17] However, evidence-based studies regarding an optimal perioperative hemostatic dose regimen are still lacking. A literature search revealed different dose recommendations of this drug for surgical patients with loading doses ranging from 10 mg/kg to 20 mg/kg and maintenance doses ranging from 0.25 mg/kg/h to 2 mg/kg/h, boluses delivered at regular time intervals, and infusions continued till the end of the surgery, all showing variable effects on perioperative blood loss.[16,18-22] A bolus dose of 10 mg/kg of tranexamic acid maintains hemostatic plasma concentrations of tranexamic acid for up to 3 h,[23] but higher doses can lead to intravascular thrombosis and seizure-like activity.[24] Low-dose continuous infusions followed after the bolus can therefore avoid the risk of thrombosis or seizures and yet maintain therapeutic concentrations of the drug required to reduce blood loss.

Solid tumors are known to be associated with increased plasma levels of fibrinogen, fibrin-related antigen, and fibrinopeptide A.[25] These factors can potentially cause an inadequacy of plasma levels of tranexamic acid in the early postoperative period in oncosurgical procedures, particularly in the first 6–8 h after surgery, thus demanding extension of antifibrinolytic activity in the same period.

This study was conducted with an aim to investigate the effect of two drug dose regimens of tranexamic acid in reducing perioperative blood loss and their influence on the requirement of allogenic blood transfusion in abdominal tumor surgery. Our hypothesis was that a low dose tranexamic acid infusion continued in the postoperative period would produce better perioperative hemostasis.

Material and Methods

A prospective, randomized, double-blind study was carried out after the institutional ethics committee approval.

After obtaining informed consent, 60 adult, American Society of Anaesthesiologist's classification physical status 1 and 2 patients, both males and females, electively posted for open abdominal tumor surgery in the department of surgical oncology were included as study population. Patients with a history of bleeding diathesis, pulmonary embolism or deep vein thrombosis, those posted for hepatic resection or liver surgery, those posted for laparoscopic tumor removal, and those with a known allergy to tranexamic acid were excluded from the study. Oral anticoagulants and nonsteroidal anti-inflammatory drugs were stopped one day before the surgery. The study population was randomly assigned by a computer-generated randomization table to the following three groups (20 patients each),

Group A: single bolus dose of tranexamic acid (10 mg/kg) 10 min prior to incision (bolus group) followed by normal saline infusion through syringe pump till 4 h postoperatively.

Group B: single bolus dose of tranexamic acid (10 mg/kg) 10 min prior to incision followed by infusion of tranexamic acid through syringe pump (1 mg/kg/h) till 4 h postoperatively (infusion group).

Group C: single bolus of normal saline followed by normal saline infusion through syringe pump (control group).

The drug infusions were prepared by a person who had access to the computer-generated table but was not involved in data collection or patient management perioperatively. Data collection was carried out by a person who was completely blinded to the randomization. The person who analyzed the data statistically was not involved in randomization or data collection. Total volume of the composed drug formulation and placebo (normal saline), wherever required, was kept similar in the three groups to achieve effective blinding.

Baseline values of hemoglobin and hematocrit level were noted preoperatively. All the patients received general anesthesia. The patients received IV glycopyrrolate (15 g/kg), fentanyl citrate (2 g/kg) and pantoprazole (0.8 mg/kg) as premedication, thiopentone sodium (5–7 mg/kg) for induction and rocuronium bromide (0.6 mg/kg) for intubation. Thereafter they received fentanyl citrate (0.3 g/kg/h), atracurium (0.5 mg/kg/h) as intravenous infusions along with isoflurane, the dial concentration of which was adjusted to maintain a mean arterial pressure within 20% of the baseline reading.

Intraoperative monitoring included pulse oximetry, 5 lead electrocardiograph, capnography, urine output, core

temperature, invasive blood pressure, and central venous pressure. Arterial blood gas analysis was done, as and when required, to monitor blood gases, electrolytes, and blood sugar. Epidural analgesia was used for pain relief which was continued in the postoperative period till one day.

Total volume of intravenous fluids infused and whole blood units or blood products transfused were noted. Total duration of surgery in minutes (from skin incision to skin closure) was noted.

Intraoperative blood loss was the primary outcome which was assessed by subtracting the volume of 0.9% saline used as intra-abdominal rinse (or wash) from collection in the suction apparatus and also by counting the number of 75% soaked sponges by visual assessment. (size 30×30 cm saline soaked cotton laparotomy sponges were used for all the surgeries). According to available literature, the mean absorptive volume at 75% saturation of a 30×30 cm saline soaked laparatomy sponge has been estimated to be 75–80 ml.[26] As wetting of the above stated sized sponge reduces the absorptive capacity of the sponge by 25–30%,[26] 1 soaked sponge was taken as 50 ml of blood loss for calculation. A transfusion trigger for blood loss of more than 20% of total blood volume or hemoglobin concentration less than 8 g/dl, whichever was less, was followed in all the cases. The decision to transfuse allogenic blood was made by the same attending consultant anesthesiologist in all the cases on the basis of the transfusion triggers.

Postoperative blood loss was assessed by collection in the drain at the end of 6 h, at the end of 24 h, and from 24–48 h postoperatively (2nd day). Hemoglobin and hematocrit levels were also recorded 6 h after surgery, 24 h, and 48 h postoperatively.

Patients were monitored clinically for evidence of deep vein thrombosis (DVT) twice daily till discharge. They were assessed for calf swelling, tenderness, and edema of the leg on clinical examination. All the patients were started on daily thromboprophylaxis for DVT from the 1st postoperative day with enoxaparin 40 mg administered subcutaneously. Patients were monitored for convulsions or seizure-like episodes in the postoperative period till discharge.

Sample size calculation

On the basis of the findings in four similar studies,[19,27-29] to detect a mean difference of 225 ml in the intraoperative blood loss between the three groups, with a standard deviation of 200 ml, a sample size (N) of minimum 57 was calculated, keeping a power (1-β error probability) of 0.95 and effect size of 0.54 using F-tests-analysis of variance (ANOVA) and G

power 3.1.9.2 software. The sample size was subsequently rounded off to 60 (20 in each group).

Statistical analysis was done by using ANOVA test to find significance of the study parameters showing normal distribution within the three groups, Post-Hoc Tukey (two-tailed, independent) to find the significance of study parameters on continuous scale between the groups (intergroup analysis), and Kruskal–Wallis test to find the significance for nonparametric distribution, using SAS 9.0 (SAS institute, North Carolina State University, USA), SPSS15.0 (IBM corporation, New York, United States), Stata10.1 (StataCorp LLC, Texas, USA), and R environment ver. 2.11.1 statistical software. Significance was assessed at a level of 5% ($P < 0.05$). Microsoft Excel was used to generate graphs and tables.

Results

Demographic data and the mean duration of surgery, which were taken as the time from surgical incision to surgical closure, were comparable in all the three groups, as shown in Table 1. The types of surgeries performed in the three groups are presented in Table 2.

Total intraoperative blood loss was similar in all the three groups [Table 3]. Both the tranexamic acid groups showed statistically significant reduction in the mean postoperative drain collection at 24 h in comparison to the control group. There was also a highly significant difference in the postoperative drain at 24 h within the tranexamic acid groups, where lesser collection was seen in the infusion group (Group B) (*post hoc* Tukey–Kramer analysis; $P = 0.017$). Drain collections in all the three groups were similar between 24-48 h postoperatively, with no statistical difference within the groups [Table 3].

There was no significant difference in hemoglobin levels at 6, 24, and 48 h in the two tranexamic acid groups when compared with their baseline values. However, there was a statistically significant reduction in hemoglobin at 6, 24, and 48 h between the three groups. These differences in hemoglobin were statistically significant but not clinically significant. Similar results were reflected as hematocrit values at different time intervals [Table 4].

Out of the total 6 blood transfusions given in the intraoperative period, 4 transfusions were given in patients of the group C and one each in both Group A and Group B ($P = 0.344$). There was no incident of allergic reaction, perioperative thromboembolic event, postoperative calf tenderness or any postoperative convulsions or seizure-like activity.

Discussion

In our study, the use of tranexamic acid by both the techniques did not significantly affect intraoperative blood loss when compared to the placebo group, a finding similar to a few more studies.[16,17,19,30] It has been observed that tranexamic acid predominantly reduces postoperative blood loss by capillary ooze owing to its antifibrinolytic activity rather than reducing active bleeding, and our results assert the observation.[31]

However, its use significantly reduced postoperative bleeding in our patients when compared to placebo, resulting in better preservation of hematological indices. Our results were comparable to studies where similar parameters were used to assess blood loss in different types of surgeries with the intraoperative use of tranexamic acid.[5,8,9,13,16,17]

Table 1: Distribution of patients according to demographic data

	Demographic data (n=60)			
	Group A (n=20)	Group B (n=20)	Group C (n=20)	P
Mean age (years)	45.9±8.8	47.2±11.1	49.3±8.6	0.53
Male:female	5:15	8:12	5:15	0.52
Mean weight (kg)	58.4±6.3	56.9±7.8	55.3±5.3	0.32
ASA status (1:2)	13:7	8:12	13:7	0.18
Mean duration of surgery (min)	255.0±82.6	260.5±67.6	241.5±74.1	0.8

Values in mean±SD and ratio

Table 2: Distribution of patients according to type of surgery performed

	Type of surgery		
Name of surgery	Group A (n=20)	Group B (n=20)	Group C (n=20)
Bilateral adrenalectomy	1	0	0
Abdominoperineal resection	2	3	2
Hemicolectomy	3	2	3
Uterine myomectomy	0	1	0
Radical nephrectomy	2	1	2
Radical cystectomy	2	3	3
Hysterectomy	8	8	6
Pancreatectomy	0	1	1
Sigmoidectomy	2	1	3

Values in numbers

We used tranexamic acid in two different ways, as a single bolus dose and as an infusion continued in the early postoperative period after a single dose bolus. There was a significant difference in postoperative bleeding at the end of 24 h with the continuous infusion when compared with the single bolus method. A single bolus dose of tranexamic acid of 10 mg/kg produces a therapeutic plasma concentration of 5–10 µg/ml which lasts only for three hours.[23] The effect of a larger dose (20 mg/kg) lasts for approximately 8 h, but carries the potential risk of thrombotic activity which can pose a greater threat to the well-being of the patient.[24] Repeated boluses at regular time intervals may not produce uniform plasma concentrations resulting in unpredictable antifibrinolytic activity.[32] The early postoperative period is marked by increased release of tissue plasminogen activators resulting in increased fibrinolysis,[33] and is thus, the time when optimum levels of antifibrinolytic activity are required. Therefore, we postulated that a low-dose continuous infusion extending into the early postoperative period would make a significant difference in the management of hemostasis and our results affirmed this. The dose of tranexamic acid in our study was based on a regimen used by a similar study carried out in a population undergoing hip arthroplasty procedures.[33] Hepatic tumor resection is known to be associated with variable hyperfibrinolytic states.[34] Therefore, anticipating variable results, we excluded liver tumor surgeries from our study population.

Tranexamic acid in higher doses (above 45 mg.kg^{-1}) has been associated with postoperative seizures, and the two traditionally hypothesized reasons for this proconvulsant activity are: (1) cerebral vasospasm or cerebral artery thrombosis and (2) inhibition of ɣ amino butyric acid-A receptors in the brain.[35-38] The total dose used in our study was smaller than 45 mg.kg^{-1} and none of our patients showed this complication.

Literature suggests the theoretical possibility of a hypercoagulable state with the use of tranexamic acid.[39] There was no evidence of DVT in the postoperative period in our study population, a finding similar to some more similar studies included in a large meta-analysis.[33,40]

Table 3: Intra-operative and Postoperative blood loss in milliliters (ml) at different time intervals in the three groups

Intraoperative	Group A (n=20)	Group B (n=20)	Group C (n=20)	95% CI P value
6 hours	33.3±14.1	27.3±10.2	49.5±12.3	(−1.97, 10.80) 0.26
24 hours	56.9±16.2	39.0±12.4**	73.0±20.0	(0.89, 12.47) 0.02*
24-48hours	11.3±9.6	7.9±6.4	10.0±12.7	(−12.6, 0.22) 0.1

For parametric data P value was calculated by one-way ANOVA; for nonparametric distribution P value was calculated by Kruskal–Wallis test, (**P=0.017 by post-hoc analysis Tukey–Kramer between group A–Group B at 24 hours); values in mean±SD

Table 4: Hematologic indices in the three groups at different time intervals

Time interval	Group A (n=20)	Group B (n=20)	Group C (n=20)	P
Baseline				
Hb (g/dl)	10.7±1.6	11.8±1.8	11.0±1.8	0.132
Hct (%)	31.1±4.1	33.1±6.3	31.9±5.6	0.490
6 hours postoperative				
Hb (g/dl)	10.2±1.3	10.8±1.3	9.1±1.0*	0.001*
Hct (%)	30.9±6.3	33.5±4.2	28.2±3.4*	0.001*
24 hours postoperative				
Hb (g/dl)	10.5±1.1	10.8±1.3	9.7±0.8*	0.005*
Hct (%)	31.6±3.3	33.0±4.2	28.1±2.3*	0.001*
24-48 hours postoperative				
Hb (g/dl)	10.6±0.9	10.8±1.2	9.5±1.1*	0.003*
Hct (%)	31.9±2.7	32.5±3.7	29.0±2.6*	0.009*

*For parametric data P value was calculated by one-way ANOVA; for nonparametric distribution P value was calculated by Kruskal–Wallis test, (*P=<0.01 by post-hoc analysis Tukey–Kramer between Group A–Group C, Group B–Group C at 6, 24, and 24-48 hours); values in mean±SD*

We estimated perioperative blood loss by the visual estimation method, that is, by measuring collection in the suction apparatus and drain and by counting the number of soaked sponges intraoperatively. Methods such as gravimetric estimation (photometric estimation) and other miscellaneous methods (e.g., mathematical calculation, use of a visual analogue scale etc.) have been documented in literature with varying accuracy.[41,42] We chose this method in our study owing to the lack of availability and practicality of other more accurate methods.

Limitations

Our study was not devoid of limitations. The use of thromboelastography in addition to hematological indices could have made our data even more complete and accurate. Second, the method of assessment of perioperative blood loss which we used was crude and subject to potential variability from observer to observer. Third, we relied on clinical signs and symptoms of DVT, where radioimaging with an ultrasonic Doppler would have perhaps picked up the most initial stages of thrombosis if any were to occur.

Conclusion

We thus conclude that tranexamic acid more effectively reduces blood loss when used as a bolus followed by an infusion continued in the postoperative period in comparison to its use as a single intravenous bolus in abdominal tumor surgery.

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Conflicts of interest
There are no conflicts of interest.

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