Original Article

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# A Randomized Comparison of Two Doses of Tranexamic Acid in High-Risk Open-Heart Surgery

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## Abstract

**Background and aims:** Tranexamic acid is commonly used in cardiac surgery to minimize perioperative bleeding. There are wide variations in dose of this drug. This study aims to find out the minimal effective dose of tranexamic acid.

**Methods:** Patients were randomized into low dose group receiving 10 mg/kg and high dose group receiving 30 mg/kg bolus of tranexamic acid each followed by an infusion of 1mg/kg/hr until the end of surgery. Primary objective was to compare blood loss during the first postoperative day. Secondary objectives were to compare total blood products transfused during 24 hours post-operative period, to compare the incidence of re-explorations and to compare the adverse drug reactions between the groups.

**Results:** There were sixty patients in each group. There was a significant difference in blood loss (435.17± 299.91 ml vs 528.64 ±254.04 ml) between the low dose group and High dose group (p=0.010). Transfusion of packed red blood cell, re-exploration and adverse drug reactions were higher in high dose group however these were not statistically significant.

**Conclusion:** Higher dose of tranexamic acid is not effective in reducing blood loss in open heart surgery in first postoperative day.

**Keywords:** Fibrinolysis, Open heart surgery, Tranexamic acid

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## Introduction

Perioperative bleeding is a common complication during cardiac surgery increasing morbidity and mortality.[1,2] Bleeding in cardiac surgery may be due to use of cardiopulmonary bypass (CPB), platelet dysfunction, impaired coagulation, use of heparin and hyperfibrinolysis.[3,4,5] Increased duration of cross clamp time during cardiopulmonary bypass correlates directly with increased bleeding.[6] Current clinical practice guidelines recommend use of tranexamic acid in cardiac surgery.[7] The significance for its use is more for the cardiac surgery with higher risk of bleeding like aortic valve surgery, coronary artery bypass grafting, redo surgeries and surgeries with prolonged CPB time.[8] However, there is wide variation in the dose of tranexamic acid ranging from 10mg/Kg to 100mg/kg.[9] The higher dose of this drug is associated with seizures and thromboembolic events.[10,11] The objective of this study was to find out the minimal effective dose of tranexamic acid in high-risk open-heart surgeries in terms of bleeding and transfusion requirement.

## Methods

This is a single-center, double-blinded, randomized controlled trial conducted in a tertiary cardiac center of Nepal. The study was approved by the Ethical Review Board, National Health Research Council of Nepal (Ref no 2394). The study was also registered in clinicaltrial.gov (ClinicalTrials.gov ID: NCT04996368). All patients received detailed verbal and written consent during the pre-anesthetic evaluation on the day before the surgery. The population of the study was the patients undergoing open heart surgery during the five months period in the year 2021-2022 AD. From the study by Sigaut S et al, mean blood loss in low dose group was 820 ±50.7 ml while that was 590 ± 50.4 ml high dose group.[12] So, the pooled standard deviation was 50.55 (σ). Now considering a type I error of 0.05% (α) and power of 80% (type II error i.e. β=0.2); confidence coefficients Zα/2=1.96 and Zβ=0.84. We desired a precision of 27 ml (d=27) i.e., our study will detect a difference in blood loss as low as 27 ml. N= $2 (Z\alpha/2 + Z\beta)^2 \times \sigma^2 / d^2$. Therefore N= $2 (1.96+0.84)^2 \times 50.552/ (27)^2 = 54.96 \sim 55$. Taking into account, 10 % possible risk of dropout, we took 60 sample size in each group. Inclusion criteria were the patients with age more than 18 years scheduled for cardiac surgery CPB with total cross clamp time of more than 60 min. The exclusion criteria included patients with allergy to tranexamic acid or any of the lysine analogues, history of seizure, chronic homeostasis abnormality, platelet <100000/cc, prothrombin time (PT) >20sec, international normalized ration (INR) >2, on anticoagulant, severe chronic kidney disease with creatinine clearance less than 30ml/hr and deranged liver function test.

### Operative procedure

After pre-anesthetic evaluation and obtaining consent, those patients fulfilling the inclusion criteria were randomly assigned by sealed envelope method into two groups: Low dose group and high dose group. Low dose (L) group received 10 mg/kg of tranexamic acid intravenous (IV) bolus while high dose (H) group received 30 mg/kg bolus. Each bolus dose was given before induction of anesthesia or immediately after induction but before the skin incision. Each bolus dose was followed by infusion of tranexamic acid at 1 mg/kg intravenous infusion till the surgery was completed with final skin closure. All drugs were prepared by anesthesia assistant not involved in the study. Induction of anesthesia was done as per institutional protocol. We monitored electrocardiogram (ECG), Spo2 and opened intravenous access with 16G IV canula. Arterial line was opened using 20G arterial cannula. Central venous catheter was inserted either before or after the induction of anesthesia depending on the anesthetist's comfort. Induction was done with balanced anesthetic using midazolam, fentanyl, propofol and vecuronium and maintained with isoflurane. During cardiopulmonary bypass, anesthesia was maintained with propofol infusion. Foleys catheterization was done after the induction of anesthesia. Besides that, end tidal carbon dioxide and temperature monitoring was done in all cases. Before CPB, all patients received 400 U/kg dose of heparin, and if necessary additional doses were given to achieve and maintain an activated clotting time (ACT) greater than 480 seconds during CPB. CPB pump flow was adjusted to maintain a mean arterial pressure greater than 60 mmHg. Temperature during CPB was maintained above 30°C. Weaning from CPB was augmented by inotropes, vasopressors or intra-aortic balloon pump (IABP) as indicated. After discontinuation of CPB, heparin was reversed with protamine sulfate (at a 1:1 ratio) to return the activated clotting time to within 10% of the pre heparin level. Additional dose of protamine was added if ACT was higher. Transfusion of tranexamic acid was continued until the skin closure was completed.

### Criteria for postoperative transfusion and re-exploration

Post operative transfusion criteria and re-exploration criteria were standardized. Packed red blood cells (PRBCs) were transfused if the hemoglobin concentration was less than 8 g/dl and or the hematocrit concentration was less than 24%. If the patients had signs and symptoms of hypovolemia (tachycardia, hypotension) with low mixed venous or central venous saturations and or raised lactate levels, patients with higher hemoglobin (8 to 9gm/dl) could be considered for transfusion in case of ongoing blood loss. Fresh frozen plasma was infused if the prothrombin time was higher than 1.5 times the basal value in a diffusely bleeding patient. Platelet concentrates were transfused in a bleeding patient with platelets count less than 50000/cc. Surgical re-exploration was done if blood loss in surgical drain was greater than 300 ml/hr for first two hours or was greater than 200 ml/h for 4 consecutive hours with normal coagulation profiles.

### Assessment of adverse effects

During the first 24 hour in ICU, the possible thrombotic complications due to tranexamic acid were recorded. Myocardial infarction (defined as new Q waves in ECG, significant raise in myocardial enzymes, new regional wall motion abnormality)[13], acute renal insufficiency (defined as a creatinine value twice that of the baseline)[14], major neurologic dysfunction (transient ischemic attack or cerebrovascular injury), deep venous thrombosis, and pulmonary embolism. Clinical assessment of neurologic function was performed during awakening of the patients by the intensivist.

### Statistical methods

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables presented as frequency and percentage. Shapiro Wilk test of normality was used to check the normal distribution of continuous variable. Normally distributed continuous variable between the two groups was analyzed with independent sample Student T test. Man Whitney U test was used to compare continuous variable between the two groups when normality was violated. Categorical variable between the two groups was analyzed with Pearson's Chi-Square test.

## Results

There was no significant difference in age, weight, height, baseline hemoglobin, baseline platelets, baseline prothrombin, American Society of Anesthesiologists physical status (AS-PS) and gender wise distribution between the low dose group and high dose group (p>0.05).

**Table 1 Characteristics of patients.**

| Variable | Low dose group | High dose group | P value |
|---|---|---|---|
| Ag (mean ± SD) Yrs | 52.45 ± 13.79 | 51.20 ± 12.56 | 0.644£ |
| Weight (mean ± SD) kg | 60.60 ± 12.94 | 57.50 ± 10.82 | 0.138ǂ |
| Height (mean ± SD) cm | 159 ±9.68 | 156.79±7.97 | 0.086ǂ |
| Baseline Hb (mean ± SD) gm% | 13.59±1.67 | 13.13±1.87 | 0.142ǂ |
| Baseline Platelet (mean ± SD) | 2,28,540±78,151 | 2,57,920±207340 | 0.583£ |
| Baseline Prothrombin (mean ± SD) sec | 11.00±1.25 | 11.30±1.81 | 0.577£ |
| ASA-PS III/ ASA-PS IV (n) | 52/8 | 49/11 | 0.309$ |
| Gender Male/ Female (n) | 39/21 | 42/18 | 0.599$ |

*[ǂ] Independent sample T test. [£] Man Whitney U test. [$] Pearson chi square test. [€] Fisher exact test.*

There was no significant difference in total heparin dose, total protamine dose, ACT before heparin, ACT after heparin, pump time, total cross clamp time and ACT after protamine between the low dose group and high dose group (p>0.05). There was a significant difference in blood loss (435.17±299.91 ml vs 528.64±254.04 ml) between the low dose group and High dose group (U=1306.5, p=0.010).

**Table 2 Intraoperative drugs dosing and parameters**

| Variable (mean ± SD) | Low dose group | High dose group | P value |
|---|---|---|---|
| Total heparin dose in Unit | 24,400±4790 | 23,000±4307 | 0.09[ɸ] |
| Total protamine dose (mg) | 249.13±49.33 | 234.71± 63.97 | 0.309[ɸ] |
| ACT before heparin (sec) | 149.65± 24.96 | 165.25± 84.54 | 0.141[£] |
| ACT after heparin (sec) | 645.60 ± 183.48 | 666.66± 141.82 | 0.490[£] |
| Pump Time (min) | 108.60 ± 33.84 | 113.46 ± 37.13 | 0.627[£] |
| Total cross clamp time (min) | 76.18±20.67 | 77.77±22.35 | 0.567[£] |
| ACT after protamine (sec) | 169.68 ± 146.74 | 144.12 ±20.78 | 0.513[£] |
| Total blood loss (ml) | 435.17± 299.91 | 528.64 ±254.04 | 0.010[£] |

*[£] Man Whitney U test, [ɸ]Independent Sample T test*

There was no significant difference in the distribution of type of surgery between the two groups ($\chi^2$=6.02, p=0.304).

**Table 3 Types of surgery**

| Surgical procedure | Low dose group | High dose group | Total | P value |
|---|---|---|---|---|
| CABG | 35 | 32 | 67 | 0.304[$] |
| Double valve surgery | 10 | 10 | 20 | |
| mitral valve surgery | 7 | 11 | 18 | |
| aortic valve surgery | 5 | 5 | 10 | |
| valve with CABG | 3 | 0 | 3 | |
| Other | 0 | 2 | 2 | |
| Total | 60 | 60 | 120 | |

*$ Pearson chi square test.*

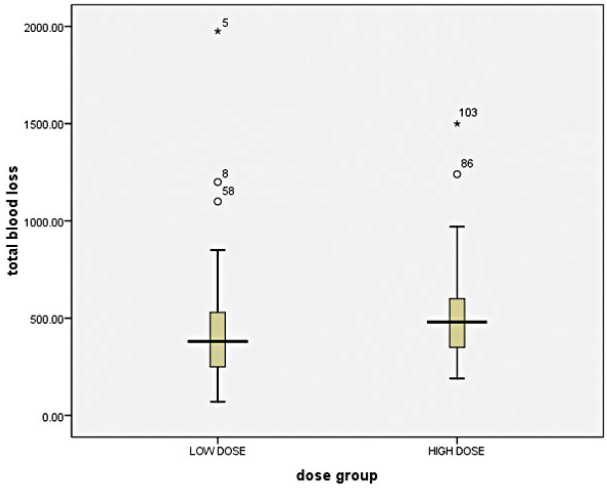


*Figure 1: blood loss in first 24 hours*

There was no significant difference in post-operative parameters: hemoglobin after 6, 12, 24 hours; platelet after 6, 24 hours between the two groups (p>0.05). There was also no significant difference in re-exploration for hemostasis; renal dysfunction and seizure between the two groups(p>0.05).

**Table 4 Postoperative Parameters and outcome**

| Variable | Low dose group | High dose group | P value |
|---|---|---|---|
| Hb after 6 hours (mean ± SD) gm% | 10.98 ± 1.58 | 10.81 ± 1.74 | 0.593[ɨ] |
| Hb after 12 hours (mean ± SD) gm% | 10.40 ± 1.38 | 10.62 ± 1.80 | 0.444[ɨ] |
| Hb after 24 hours (mean ± SD) gm% | 9.99± 1.42 | 10.24± 1.33 | 0.315[ɨ] |
| Platelet count in 6 hours (mean ± SD) | 159,640 ± 69012 | 166,830±62014 | 0.504[ɨ] |
| Platelet count in 24 hours (mean ± SD) | 168,300 ±12907 | 170,550±127790 | 0.977[ɸ] |
| Re-exploration for hemeostasis (Number of outcome) | 6 | 9 | 0.408[$] |
| Renal dysfunction (number of outcome) | 0 | 3 | 0.244[€] |
| Seizure during first week (Number of outcome) | 0 | 3 | 0.244[€] |

*[ɨ] Independent sample T test. [$] Pearson chi square test. [€] Fisher exact test.*

There was no significant difference in total RBC transfused, total FFP transfused and total PRP transfused between the two groups (p>0.05).

**Table 5 Blood products transfusion**

| Variable (mean ± SD) | Low dose group | High dose group (unit) | P value |
|---|---|---|---|
| Total RBC transfused (unit) | 0.50 ± 1.04 | 0.60 ±0.86 | 0.216£ |
| Total FFP transfused (unit) | 0.41± 0.88 | 0.28± 0.64 | 0.565£ |
| Total PRP transfused (unit) | 0.05± 0.21 | 0.05 ±0.38 | 0.323£ |

£ *Man Whitney U test.*

## Discussion

Antifibrinolytic drugs are frequently used in cardiac surgery to prevent bleeding. Two drugs, Tranexamic acid (TA) and Aminocaproic acid are the commonly used drug. They are synthetic, lysine analogue and binds to lysine binding sites of plasminogen.[15] This inhibits the plasmin formation from plasmin and also inhibit plasmin directly. TA is more potent than Aminocaproic acid.[16] However, optimal dosing and timing of tranexamic acid remained controversial. There are no clear recommendations regarding the dose of tranexamic acid that perfectly balances its antifibrinolytic activity and adverse effects. There are many factors triggering the fibrinolytic activities during cardiopulmonary bypass, which varies with duration of aortic cross clamp and CPB duration. Single pre-incision dose may not be effective.

We initially conducted a pilot study in relatively low risk groups like single valve surgery and closure of atrial septal defect with aortic cross clamp time less than sixty minutes. That showed no difference in terms of blood loss, re-exploration and adverse effects in first 24 hours. This encouraged us to conduct study in relatively high-risk surgeries like multivessel CABG, double valve surgeries, complicated single valve surgeries with like cross clamp time more than sixty minutes. Furthermore, we excluded those surgeries that are very high risk in terms of bleeding like major aortic surgeries, redo surgeries, surgeries needing intraoperative transfusion because of excessive surgical bleed and those surgeries with aortic cross clamp time more than 150 minutes.

We had very much homogeneous population of patients in terms of age, sex, height, weight, ASA PS, types of surgery and duration of surgery. Our study showed a statistical difference between low dose and high dose groups in post operative bleeding in first 24 hours. However, there was no statistical difference in transfusion of blood products and adverse effects such as renal, neurological or thromboembolic events. Furthermore, there was no statistical significance in level of hemoglobin, platelets counts and re-exploration in first 24 hours.

In the similar study conducted by Sigaut et al where low dose of 10mg/kg bolus of TA followed by 1 mg·kg−1·h−1 infusion until the end of surgery compared with high dose of 30mg/kg bolus followed by 16 mg·kg−1·h−1 infusion.[12] They found significantly less blood loss in the high-dose group during the first 24h after surgery (820±50.7 vs. 590±50.4ml; P = 0.01). Similarly mean amount of blood products transfused during surgery and up to 7 days after surgery was lower in the high-dose group which is statistically significant (4.1±0.39 versus 2.5±0.38; P = 0.02). They have significantly lesser transfusion of FFP, Platelet concentrate and fibrinogen. This increase in requirement of blood products in the study of Sigaut et al unlike our study may be because of four reasons. First excluded all cases requiring intraoperative blood transfusion because of surgical complications. Second, we excluded all cases that required cross clamp time more than 150 minutes as they are more likely to develop coagulopathy. Third we followed case only for 24 hours considering that this is the high-risk period requiring careful hemostatic management. Fourth reason was that they have included the cases high risk transfusion like patients receiving dual antiplatelet anytime within 5 days of surgery, redo surgeries and surgery of aorta. This may be the reason that the re-exploration rate in the study of Sigaut et al was significant between the two groups while (2.5 vs. 6%, p-0.01) while our study did not have significant re-exploration rate.

In the recent study by Shi et al where he compared high dose of 30mg/kg bolus followed by 16mg/kg/hr infusion with 2mg/kg prime and low dose of 10mg/kg bolus followed by 2mg/kg/hr maintenance with 1mg/kg prime.[17] They found that allogenic red blood cell transfusion was 21.8% in high dose group while 26.0% in low dose group (p=0.04). The composite 30 days adverse effects of postoperative seizure, thrombotic events, kidney dysfunction, and death occurred in 17.6% in high dose group and 16.8% in low dose group (p=0.03). Unlike the study of Shi et al, we didn't give TA in pump prime and also intraoperative infusion was 1mg/kg/hr. In 24-hour, observation of our study, we didn't observe seizure, kidney dysfunction or thrombotic events in low dose group while composite adverse effects in high dose group was only 0.1% which is not significant. This lesser adverse events in our study were may be due to relatively low risk group of patient population and lesser observation period.

Another similar study by Du et al where they were using 10mg/kg bolus plus maintenance of 2mg/kg/hr and prime dose of 40mg in low dose group while high dose group were receiving30mg/kg bolus plus 16mg/kg/hr maintenance and prime dose of 2mg/kg.[18] Unlike the finding of our study along with finding of the study of Sigaut et al and Shi et al, they found no significance difference in 24 hour post operative blood loss, amount of allogenic blood transfusion, mortality and morbidity.

Myles et al conducted a large randomized controlled trial on 2 by 2 factorial design among the patients undergoing coronary artery surgery.[19] The participants were assigned as Aspirin (100mg) vs normal saline and Tranexamic Acid (initially at dose of 100mg which later changed to 50mg) vs normal saline. They found significantly lower bleeding in TA group compared to placebo without increase in mortality or thrombotic complications within 30 days of surgery. However, there was increase in incidence of postoperative seizure in TA group. In a model-based metanalysis by Zufferey et al to find the different doses of TA on postoperative bleeding and clinical seizures.[20] They included 64 randomized controlled trials and 18 observational studies of TA in cardiac surgeries. They concluded that low-dose TA (total dose of 20mg/kg of actual body weight) balances the risk versus benefit of postoperative blood loss, red blood cell transfusion and the risk of clinical seizure. In another metanalysis by Guo et al including 49 studies of TA in cardiac surgeries[8]. Among the 49 studies (10591 patients) 36 of them were trials with 14 of the trials using only bolus regimen while remaining 22 trials used bolus followed by continuous infusion. They concluded that TA reduces transfusion requirement in all kinds of cardiac surgeries. Low-dose of 10mg/kg bolus followed by infusion of 1mg/kg (50mg/kg in case of bolus only) was the most preferable regimen which was as effective as high-dose regimen in reducing transfusion rate without increasing the risk of seizure.

Strength of our study is the homogeneous sample. We excluded all cases with cross clamp time less than 60 minutes and more than 150 minutes. This is our attempt to make homogeneous patient population in terms of risk of bleeding due to duration of bypass time. We also excluded all cases with intraoperative surgical complications requiring transfusions. There are some limitations in our study. Our sample size in low. The clinical outcomes are not powered. We followed up cases only for 24 hours. We thought that first 24 hours following the surgery is very crucial period in terms of bleeding due to fibrinolysis.

In conclusion, TA with high dose regimen of bolus dose of 30mg/kg followed by infusion 1mg/kg/hr is not effective in terms of reducing blood loss when compared to low dose regimen of 10mg/kg bolus followed by 1mg/kg/hr infusion.

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**Conflicts of interest**

There are no conflicts of interest.

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