Original Article

# A comparison of high-dose and low-dose tranexamic acid antifibrinolytic protocols for primary coronary artery bypass surgery

**Address for correspondence:**
Dr. Kathirvel Subramaniam,
Department of Anesthesiology,
University of Pittsburgh,
Pittsburgh, PA 15213, USA.
E-mail: kas338@pitt.edu

*Stephen M McHugh, Lavinia Kolarczyk[1], Robert S Lang[2], Lawrence M Wei[3], Marquez Jose, Kathirvel Subramaniam*

**Departments of Anesthesiology and [3]Cardiac Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, [1]Department of Anesthesiology, University of North Carolina at Chapel Hill, NC, [2]Department of Anesthesiology, Children Hospital of Pittsburgh, Pittsburgh, PA, USA**

**Access this article online**

Website: www.ijaweb.org

DOI: 10.4103/0019-5049.176279

Quick response code

## ABSTRACT

**Background and Aims:** Tranexamic acid (TA) is used for prophylactic antifibrinolysis in coronary artery bypass surgeries to reduce bleeding. We evaluated the efficacy of two different doses of TA for prophylactic antifibrinolysis in patients undergoing primary coronary artery bypass grafting (CABG) surgery in this retrospective cohort study at a tertiary care referral centre. **Methods:** One-hundred eighty-four patients who underwent primary CABG with cardiopulmonary bypass (CPB) via sternotomy between January 2009 and June 2011 were evaluated. Pre-operative patient characteristics, intraoperative data, post-operative bleeding, transfusions, organ dysfunction and 30-day mortality were compared between high-dose TA (30 mg/kg loading dose followed by infusion of 15 mg/kg/h until the end of surgery along with 2 mg/kg priming dose in the bypass circuit) and low-dose TA (15 mg/kg loading dose followed by infusion of 6 mg/kg/h until the end of surgery along with 1 mg/kg priming dose in the bypass circuit) groups. Univariate comparative analysis of all categorical and continuous variables was performed between the two groups by appropriate statistical tests. Linear and logistic regression analyses were performed to control for the effect of confounding on the outcome variables. **Results:** Chest tube output, perioperative transfusion of blood products and incidence of re-exploration for bleeding did not differ significantly ($P > 0.05$) between groups. Post-operative complications and 30-day mortality were comparable between the groups. The presence of cardiogenic shock and increased pre-operative creatinine were found to be associated with increased chest tube output on the post-operative day 2 by multivariable linear regression model. **Conclusions:** Low-dose TA protocol is as effective as high-dose protocol for antifibrinolysis in patients undergoing primary CABG with CPB.

**Key words:** Antifibrinolytic, bleeding, coronary artery bypass, tranexamic acid, transfusion

## INTRODUCTION

Perioperative transfusion in patients undergoing coronary artery bypass graft (CABG) surgery is associated with multiple adverse outcomes.[1,2] Autologous blood transfusion, surgical techniques to minimise blood loss, use of antifibrinolytics and restrictive transfusion strategies should all form part of the patient blood management plan.[3] Since aprotinin was removed from the market in 2008 following its association with a strong negative mortality trend when comparing antifibrinolytics in a randomised trial, the lysine analogues, tranexamic acid (TA) and epsilon aminocaproic acid (EACA), have replaced



**How to cite this article:** McHugh SM, Kolarczyk L, Lang RS, Wei LM, Jose M, Subramaniam K. A comparison of high-dose and low-dose tranexamic acid antifibrinolytic protocols for primary coronary artery bypass surgery. Indian J Anaesth 2016;60:94-101.

aprotinin as antifibrinolytic agents during cardiac surgery.[4] The clinically used doses of TA that best reduce post-operative bleeding range widely from one- to ten-fold.[5] Literature evidence supports that TA may cause convulsions in a dose-dependent manner.[6] Therefore, it is important to determine the appropriate dose of TA that effectively reduces post-operative bleeding and need for perioperative transfusions to limit its adverse side effects. This retrospective study was conducted to evaluate and compare post-operative bleeding and perioperative transfusion requirements between patients receiving our institution's high-dose and low-dose TA protocols.

## METHODS

Institutional Review Board approved the study. Utilising data from the Society of Thoracic Surgeons (STS) National Database, patients who underwent primary CABG surgery via sternotomy with the use of cardiopulmonary bypass (CPB) from January 1, 2009, to June 30, 2011, were identified. This study period was specifically chosen because TA was the only drug used for antifibrinolysis at the hospital during this time. Aprotinin and TA both were used before 2009, and EACA replaced TA after July 2011 due to its lower cost. Patients undergoing additional procedures such as cardiac valve repair or replacement were not included. Anaesthetic technique and monitoring choices (other than standard American society of anesthesiologists (ASA)' monitors) were not standardised.

Anticoagulation for CPB was initiated with a 300 U/kg intravenous (IV) heparin for a target-activated clotting time (ACT) >400 s. A loading dose of TA was administered after heparinisation and an infusion of TA was started. The high-dose TA protocol consisted of a 30 mg/kg loading dose followed by a continuous infusion of 15 mg/kg/h until the end of surgery along with a 2 mg/kg priming dose in the CPB circuit. The low-dose TA protocol consisted of a 15 mg/kg loading dose followed by a continuous infusion of 6 mg/kg/h until the end of surgery along with a 1 mg/kg priming dose in the CPB circuit. Choice of TA dosing protocol was at the discretion of the attending anaesthesiologist. At our institution, two dose protocols existed so that the dose could be selected according to the risk of bleeding for any particular patient.

Normothermic CPB was used for all operations. Heparin was supplemented during bypass to maintain the ACT >400 s. During CPB, blood from the pump suction was filtered and returned to the venous reservoir. Heparin effect was reversed after discontinuation of CPB with IV protamine dosed at 1 mg/100 U of heparin in the initial bolus. A repeat dose of protamine (25–50 mg) was administered when ACT values were higher than pre-operative value with evidence of clinical bleeding. Blood from the operative field was salvaged, processed and re-infused via a cell-saver circuit.

The decision to transfuse packed red blood cells (PRBCs) and other blood products during the perioperative period was based on whether the patient was clinically bleeding or not. If there was no clinical evidence of bleeding, isolated laboratory abnormalities were not treated. If there was clinical bleeding, transfusion was guided by laboratory testing including haematocrit, thromboelastography, platelet (PLTS) count, prothrombin time and partial thromboplastin time. Transfusion practice guidelines included PRBC and PLTS transfusion in clinically bleeding patients to maintain the haematocrit >25% and the PLTS count >100,000/mm$^3$, respectively. Fresh frozen plasma (FFP) was transfused to maintain the international normalised ratio (INR) <1.4, and cryoprecipitate (CRYO) was administered for blood fibrinogen levels <150 mg/dL. Transfusions were recorded as units as follows: 1 U of PRBC = 300 mL, 1 U of FFP = 250 mL, 1 U of PLTS (pooled 6 pack) =300 mL and 1 U of CRYO (pooled 5 pack) =50 mL. Surgeons and anaesthesiologists made the decisions intraoperatively, and critical care physicians along with surgeons made the decisions on transfusion post-operatively.

Pre-operative information included date of surgery, demographics, comorbid conditions, cardiac status (number of diseased coronary arteries, left ventricular ejection fraction, presence of cardiogenic shock and use of an intra-aortic balloon pump), medication use (β blockers, angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, aspirin, lipid-lowering agents, anticoagulants within 48 h preceding surgery, adenosine diphosphate inhibitors within 5 days preceding surgery and glycoprotein IIb/IIIa inhibitors within 24 h preceding surgery) and laboratory data (serum creatinine, haematocrit, PLTS count and INR).

Intraoperative information included surgical urgency, duration of procedure and CPB and use of blood

products. Chest tube output on the post-operative days (PODs) 0–2 and perioperative transfusion totals constituted the primary outcomes of the study. Chest tube output data were taken from the institution's electronic medical record system, and blood product transfusion data were obtained from the STS database. Surgical re-exploration of the mediastinum was considered when bleeding in the first 2 h was >300 mL/h or >200 mL/h for 4 consecutive hours despite adequate replacement of clotting factors. Re-exploration was also performed in patients with haemodynamic instability or cardiac tamponade.

Secondary outcomes included post-operative complications, length of hospital stay, reoperations and mortality at 30 days. Patients were considered to have experienced a post-operative convulsion if their discharge summary contained a diagnosis of convulsion occurring after their CABG surgery. The definition of renal failure was based on the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease [RIFLE] criteria[7] and required a rise in serum creatinine by a factor of 3, serum creatinine level ≥4 mg/dL with at least a 0.5 mg/dL increase in 48 h, decrease in glomerular filtration rate by at least 75%, urine output <0.3 mL/kg/h for 24 h or anuria for 12 h.

Univariate analysis of categorical variables was performed using Chi-square or Fisher's exact tests where appropriate or with linear test-of-trend tests for ordinal variables. Continuous variables were analysed with the non-parametric Mann–Whitney U-test. Multivariable analysis was performed to examine the outcomes of any perioperative transfusion (logistic regression) and amount of chest tube output (linear regression), utilising TA dosage as a predictor along with potential confounding variables. $P < 0.05$ was considered significant. Data were analysed with the SPSS 20.0 statistical package (SPSS Inc, Chicago, IL, USA).

## RESULTS

One-hundred eighty-four patients underwent CABG surgery during the study period. Twenty-six patients were removed from analysis due to incomplete or non-standardised TA dosing regimens. Data of two patients who died on the POD 2 were not included due to incomplete post-operative chest tube output data. Therefore, 156 subjects were included, of which 104 received high-dose TA and 52 received low-dose TA.

Pre-operative characteristics were similar between the two groups [Table 1]. There was an increased likelihood that patients would receive the low-dose TA protocol at later dates during the study period [Table 1]. There was a trend towards longer procedure and CPB duration in the high-dose group [Table 2]. Chest tube output, transfusion of blood products and perioperative outcomes were similar between the groups [Tables 3 and 4]. There was a trend towards higher renal dysfunction in the high-dose group [Table 4].

Multivariable models were performed to determine the independent effects of potential confounding variables on the results. Logistic regression modelling showed that none of these variables significantly predicted whether a subject would receive transfusion of any blood product during the perioperative period [Table 5]. Linear regression models showed that pre-operative presence of cardiogenic shock and a greater pre-operative serum creatinine were shown to significantly predict greater chest-tube output on the POD 2 [Table 6].

## DISCUSSION

Patients undergoing CABG surgery have a significant likelihood of receiving allogeneic blood products.[8] Increasingly, the negative consequences of blood product transfusions are being recognised. Koch *et al.* showed that perioperative PRBC transfusion is the most important factor associated with post-operative morbidity and reduced 10 years survival.[1,2] Intraoperative transfusion of PRBCs has been shown to be a risk factor for post-operative low-output heart failure.[9]

TA is a synthetic analogue of the amino acid lysine and exerts its effects by blocking lysine-binding sites on plasminogen, thus preventing its conversion to plasmin. Randomised controlled trials and meta-analysis have shown that TA resulted in a significant reduction of haemoglobin loss, the median number of blood products given and reoperations after cardiac surgery as compared to placebo.[10-13] Despite the strong evidence suggesting the efficacy of TA for antifibrinolysis during CABG, the best dosing strategy to achieve this goal is not yet clear. TA boluses of 5, 3 and 1 g followed by TA infusions in patients undergoing cardiac surgery have been compared and it was found that 1 g was as effective as higher doses in reducing blood loss without any difference in adverse events.[14] Karski *et al.*[15] compared single

**Table 1: Preoperative patient characteristics**

| Patient demographics and characteristics | High-dose (*n*=104) | Low-dose (*n*=52) | *P* |
|---|---|---|---|
| Age (years)* | 63.7±11.2 | 64.5±11 | 0.66 |
| Male (%) | 76 (73.1) | 37 (71.2) | 0.85 |
| BMI† | 30 (26.5-35.2) | 29.1 (24.9-33.2) | 0.254 |
| Hypertension (%) | 75 (72.1) | 43 (82.7) | 0.17 |
| History of convulsions (%) | 2 (1.9) | 1 (1.9) | 1.00 |
| Chronic lung disease (%) | | | |
| Mild | 10 (9.6) | 6 (11.5) | 0.808 |
| Moderate | 2 (1.9) | 5 (9.6) | |
| Severe | 5 (4.8) | 0 (0) | |
| Cerebrovascular disease (%) | 10 (9.6) | 9 (17.3) | 0.197 |
| Peripheral vascular disease (%) | 19 (18.3) | 11 (21.2) | 0.672 |
| Diabetes mellitus (%) | 43 (41.3) | 20 (38.5) | 0.863 |
| Cardiac arrhythmia (%) | 19 (18.3) | 7 (13.5) | 0.503 |
| Dyslipidaemia (%) | 82 (78.8) | 44 (84.6) | 0.519 |
| Tobacco use (%) | 24 (23.1) | 15 (28.8) | 0.439 |
| Aspirin use (%) | 96 (92.3) | 50 (96.2) | 0.498 |
| ADP-inhibitor use (%) | 10 (9.6) | 6 (11.5) | 0.781 |
| GP IIb/IIIa inhibitor use (%) | 11 (10.6) | 1 (1.9) | 0.062 |
| Anticoagulant use (%) | 56 (53.8) | 28 (53.8) | 1.00 |
| Beta-blocker use (%) | 89 (85.6) | 49 (94.2) | 0.182 |
| Lipid-lowering drug use (%) | 79 (76) | 34 (65.4) | 0.186 |
| ACE-I/ARB use (%) | 52 (50) | 21 (40.4) | 0.308 |
| Number of diseased coronary arteries† | 3 (3-3) | 3 (3-3) | 0.508 |
| Left ventricular ejection fraction† | 45 (30-55) | 50 (35-59.3) | 0.387 |
| Intra-aortic balloon pump (%) | 21 (20.2) | 10 (19.2) | 1.00 |
| Cardiogenic shock (%) | 7 (6.7) | 1 (1.9) | 0.27 |
| Creatinine (mg/dL)† | 1 (0.8-1.2) | 0.9 (0.8-1.1) | 0.087 |
| Haematocrit† | 38.9 (35.4-41.3) | 37.2 (33.9-40.6) | 0.168 |
| Platelets (/μL)† | 194 (170-229.8) | 190.5 (151.5-217.5) | 0.138 |
| INR† | 1.1 (1.1-1.2) | 1.1 (1.1-1.2) | 0.891 |
| Date of surgery | | | |
| January 1, 2009-June 30, 2010 | 74 (83.1) | 15 (16.9) | <0.001 |
| July 1, 2010-June 30, 2011 | 30 (44.8) | 37 (55.2) | |

*Values expressed as mean±SD; †Values expressed as median (25%-75%). All other values expressed as *n* (%). SD – Standard deviation; BMI – Body mass index; ADP – Adenosine diphosphate; GP – Glycoprotein; ACE – Angiotensin-converting-enzyme; ARB – Angiotensin receptor blockers; INR – International normalised ratio

**Table 2: Intraoperative data**

| Surgical characteristics | High-dose (*n*=104) | Low-dose (*n*=52) | *P* |
|---|---|---|---|
| Surgical urgency | | | |
| Elective (%) | 25 (24) | 11 (21.2) | 1.00 |
| Urgent (%) | 74 (71.2) | 40 (76.9) | |
| Emergent (%)* | 5 (4.8) | 1 (1.9) | |
| Procedure duration (min) | 334 (269-380.3) | 317.50 (265.5-347.5) | 0.064 |
| CPB duration (min) | 126 (103-151.5) | 111 (95.5-136) | 0.054 |

*Values expressed as *n* (%). All other values expressed as median (25-75%). CPB – Cardiopulmonary bypass

bolus administration of TA in doses of 150, 100 and 50 mg/kg before the initiation of CPB with mild hypothermia in a randomised, double-blinded study. They found an increase in bleeding in the group given 50 mg/kg and recommended a dose of 100 mg/kg of TA for minimising post-cardiotomy bleed. Considering the short biological half-life of TA, boluses should be administered every 2 h to maintain therapeutic concentrations for antifibrinolysis.[16] For this reason, it is a common practice to administer TA by infusion to achieve steady therapeutic plasma levels during the intraoperative and immediate post-operative periods.

A recently published prospective randomised study compared two TA dosing strategies (10 mg/kg bolus followed by a 1 mg/kg/h infusion compared to 30 mg/kg bolus followed by 16 mg/kg/h infusion) in both high- and low-risk cardiac surgical patients.[17] The high-dose regimen decreased transfusion requirements and the re-exploration rate after cardiac surgery compared to their lower dose regimen. However, an intermediate dose group was not included. We studied an intermediate dose regimen (15 mg/kg followed by 6 mg/kg/h) and compared this to the same high-dose protocol used by Sigaut *et al.* All of our study patients

**Table 3: Post-operative chest tube output and transfusion data**

| Postoperative haemostasis and blood product transfusions | High-dose (*n*=104) | Low-dose (*n*=52) | *P* |
|---|---|---|---|
| POD 0 (mL) | 500 (350-750) | 600 (400-750) | 0.28 |
| POD 1 (mL) | 477.5 (350-650) | 495 (350-615) | 0.912 |
| POD 2 (mL) | 270 (112.5-409.5) | 283.5 (162.5-453.8) | 0.508 |
| RBC (units) | 1.00 (0-4) | 1.50 (0-4) | 0.971 |
| FFP (units) | 0 (0-1) | 0 (0-2) | 0.512 |
| Platelets (units) | 0 (0-1) | 0 (0-1) | 0.74 |
| Cryoprecipitate (units) | 0 (0-0) | 0 (0-0) | 0.775 |
| Any blood product use perioperatively* (%) | 63 (60.6) | 31 (59.6) | 0.908 |
| Any blood product use intraoperatively* (%) | 28 (53.8) | 55 (52.8) | 1.000 |
| Any blood product use post-operatively* (%) | 27 (51.9) | 51 (49) | 0.734 |

*Values expressed as *n* (%). All other values expressed as median (25-75%).
RBC – Red blood cell; FFP – Fresh frozen plasma; POD – Post-operative day

**Table 4: Post-operative complications and outcomes**

| Postoperative morbidity and mortality | High-dose (*n*=104) | Low-dose (*n*=52) | *P* |
|---|---|---|---|
| Renal failure (%) | 11 (10.6) | 1 (1.9) | 0.062 |
| Dialysis (%) | 4 (3.8) | 0 (0) | 0.302 |
| Stroke (%) | 6 (5.8) | 0 (0) | 0.179 |
| Seizure (%) | 2 (1.9) | 0 (0) | 0.553 |
| Any reoperation during admission (%) | 12 (11.5) | 5 (9.6) | 0.792 |
| Reoperation during admission for bleeding (%) | 4 (3.8) | 3 (5.8) | 0.687 |
| Total length of hospital stay* | 7 (6-11) | 7 (6-8) | 0.176 |
| 30 days mortality (%) | 3 (2.9) | 3 (5.8) | 0.567 |

*Values expressed as median (25-75%). All other data expressed as *n* (%)

**Table 5: Logistic regression analysis for the outcome of "any blood product use perioperatively"**

| Variable | Odds ratio | 95% confidence interval | *P* |
|---|---|---|---|
| High-dose TA (vs. low) | 0.783 | 0.362-1.695 | 0.535 |
| Presence of cardiogenic shock | 1.753 | 0.322-9.539 | 0.516 |
| Pre-operative GP IIb/IIIa inhibitor use | 0.892 | 0.252-3.156 | 0.859 |
| Surgery date after July 1, 2010 (vs. before) | 0.610 | 0.293-1.271 | 0.187 |
| Pre-operative creatinine (mg/dL) | 0.978 | 0.722-1.326 | 0.888 |
| Procedure duration (min) | 1.003 | 0.995-1.010 | 0.507 |
| CPB duration (min) | 1.000 | 0.987-1.014 | 0.966 |

TA – Tranexamic acid; GP – Glycoprotein; CPB – Cardiopulmonary bypass

underwent coronary artery bypass surgery. We did not find any difference in antifibrinolytic efficacy between the two groups. The differences in the results can be explained by previous pharmacokinetic studies on TA.

Several plasma therapeutic target levels and various dosing regimens to achieve specific target levels have been suggested in the literature. Dowd *et al.* in their pharmacokinetic study suggested that a 12.5 mg/kg TA IV bolus followed by a 6.5 mg/kg/h infusion would be required to maintain therapeutic levels (334 μM [50 μg/mL]) in a typical adult cardiac surgery patient. They suggested using a higher dose (30 mg/kg bolus followed by 16 mg/kg/h) to achieve 100% suppression of fibrinolysis (plasma levels; 800 μM or 121 μg/mL) for high-risk patients.[18] A bolus of 10 mg/kg followed by a 1 mg/kg/h infusion provided therapeutic levels (10 μg/ml) required for 80% antifibrinolysis, but there were inconsistencies in another study.[19] They suggested a dosing regimen to achieve therapeutic levels of 20 μg/mL to avoid inconsistencies. They also added that plasmin-induced PLTS activation is inhibited by therapeutic TA levels at 16 μg/mL. The same group tested two different TA treatment regimens in another study.[20] The first regimen, a 10 mg/kg TA bolus followed by a 1 mg/kg/h infusion failed to achieve therapeutic levels (20 μg/mL) in a significant percentage of patients at all times (5 min after the bolus, at the onset of CPB, 30 min after CPB initiation, at the end of CPB and at the end of the TA infusion). A new treatment regimen involved a 5 mg/kg TA bolus followed by a 5 mg/kg/h infusion but failed to achieve therapeutic levels 5 min after the bolus, at the start of CPB and 30 min after the onset of CPB. Combining the results of the above studies, the patients in the current study were administered a higher bolus dose and suggested infusion rates (6 mg/kg/h) with the aim of achieving consistent therapeutic levels >20 μg/mL for better efficacy. We did not measure plasma TA levels during surgery, and our study results only apply to CABG as we did not include other high-risk cardiac surgical patients such as aortic surgery and multivalve surgery.

Selecting an appropriate dose of TA is important because several recent reports have implicated TA as the cause for post-operative convulsions, especially with higher doses (>100 mg/kg total cumulative dose).[21-23] Furthermore, patients with renal dysfunction have an increased risk of developing blood levels of TA high enough to precipitate convulsions.[24] When administered as a bolus, half of the TA dose is excreted unchanged in the urine within 3 h, 95% within 24 h and 95–99% within 48–72 h. Convulsions occurring after cardiac surgery are associated with poorer outcomes.[25] Based on their experimental study in rats, Furtmüller *et al.*[26] provided a pharmacological basis for the proconvulsant properties of TA by showing that the drug binds to and inhibits $GABA_A$ (gamma aminobutyric acid A receptors)

**Table 6: Linear regression analysis for chest tube output (mL) on post-operative day 0-2**

| Variable | Coefficients | 95% confidence interval | *P* |
|---|---|---|---|
| POD 0 | | | |
| High-dose TA (vs. low) | −53.436 | −220.00-113.127 | 0.529 |
| Presence of cardiogenic shock | −216.517 | −547.028-113.993 | 0.199 |
| Pre-operative GP IIb/IIIa inhibitor use | 135.542 | −140.377-411.461 | 0.336 |
| Surgery date after July 1, 2010 (vs. before) | 13.399 | −146.662-173.460 | 0.870 |
| Pre-operative creatinine (mg/dL) | 47.749 | −19.361-114.858 | 0.163 |
| Procedure duration (min) | 0.651 | −1.028-2.330 | 0.447 |
| CPB duration (min) | 2.31 | −0.622-5.242 | 0.123 |
| POD 1 | | | |
| High-dose TA (vs. low) | 9.388 | −147.667-166.444 | 0.907 |
| Presence of cardiogenic shock | −112.542 | −424.179-199.095 | 0.479 |
| Pre-operative GP IIb/IIIa inhibitor use | 3.704 | −255.621-263.03 | 0.978 |
| Surgery date after July 1, 2010 (vs. before) | 4.58 | −145.903-155.064 | 0.952 |
| Pre-operative creatinine (mg/dL) | 18.937 | −44.349-82.223 | 0.558 |
| Procedure duration (min) | 0.317 | −1.249-1.883 | 0.692 |
| CPB duration (min) | 1.254 | −1.51-4.017 | 0.374 |
| POD 2 | | | |
| High-dose TA (vs. low) | −64.256 | −170.921-42.409 | 0.238 |
| Presence of cardiogenic shock | 413.616 | 201.965-625.267 | <0.001 |
| Pre-operative GP IIb/IIIa inhibitor use | 4.985 | −171.138-181.108 | 0.956 |
| Surgery date after July 1, 2010 (vs. before) | 10.764 | −91.439-121.966 | 0.836 |
| Pre-operative creatinine (mg/dL) | 50 | 7.019-92.982 | 0.023 |
| Procedure duration (min) | 0.230 | −0.833-1.293 | 0.672 |
| CPB duration (min) | 0.935 | −0.942-2.812 | 0.329 |

POD – Post-operative day; TA – Tranexamic acid; GP – Glycoprotein; CPB – Cardiopulmonary bypass

receptors in the central nervous system, thus leading to hyper- excitability. Notably, accidental injections of TA into the intrathecal space resulting in convulsions have been reported.[27,28] Two patients in the high-dose group experienced convulsions post-operatively, one on POD 0 and one on POD 2. Neither of these patients had a pre-operative history of convulsions. Three patients with a history of pre-operative convulsions did not develop post-operative convulsions. Although a history of convulsion is not described as a risk factor for post-operative convulsions after TA administration, we feel in retrospect that the use of TA could have been safely avoided in those patients.

TA use has been associated with myocardial infarction, especially in settings where no anticoagulation was used.[29,30] In the present study, the TA bolus and infusion was administered after heparinisation to reduce the risk of inducing coronary thrombosis and ischaemia in patients with significant coronary artery disease. Ideal timing of TA administration is unknown since there are no studies comparing different timings of TA administration (i.e. before skin incision versus after heparinisation) on efficacy and safety. Pharmacokinetic studies have shown that therapeutic plasma levels can be achieved within 5 min of a TA bolus in the doses studied, supporting our timing of the TA bolus administration. We did not come across any incidence of myocardial infarction during surgery or graft thrombosis after revascularisation even with the high-dose regimen. The high-dose TA protocol was associated with an increased number of patients developing post-operative renal failure and stroke although none of these differences reached statistical significance. Our study was not primarily designed to detect the difference in adverse events between the two doses. Other thromboembolic events such as deep vein thrombosis and pulmonary embolism were not studied in this report. These findings on adverse events need to be confirmed by a larger study with appropriate sample size. The sample size in this study cohort could not be increased due to the finite period during which TA was used as the sole antifibrinolytic at our institution (January 2009 to June 2011).

The present study has several limitations. This was a retrospective, observational, non-randomised study. Unmeasured patient or surgical characteristics may have affected the outcomes. Because patients were not randomised between the two groups, anaesthesiologists chose a particular dose of TA thus introducing selection bias. To account for this, multivariable models were created to control for pre-operative and intraoperative variables that trended towards, but did not reach,

statistically significant differences between the high-dose and low-dose groups. These models included the date of surgery which was included because there was a higher likelihood that patients received the low-dose TA protocol after July 1, 2010. This initial preference for the high-dose protocol could be related to the opinion that higher doses of TA would result in a stronger antifibrinolytic effect. The gradual increase in use of the low-dose protocol most likely occurred as knowledge of TA's dose-related side effects including risk of convulsions became more widely appreciated. None of these variables, including the date of surgery, had significance towards predicting transfusions or chest-tube outputs on POD 0 or 1. Although the pre-operative presence of cardiogenic shock and elevated pre-operative serum creatinine did show significance towards predicting POD 2 chest-tube output, the other variables continued to show non-significance. While not eliminating the possibility of selection bias, these analyses further strengthen our conclusions.

Two patients who died on POD 2 (both in the high-dose group) were excluded to avoid artificially lowering values of chest tube output. The results of our main outcomes, post-operative chest tube output and perioperative transfusion requirements did not change when those two patients were included in the analysis. Despite the existence of guidelines for perioperative blood component transfusion therapy, transfusions were ordered by the anaesthesiologists, surgeons or intensivists caring for the patients and there may have been variations from the guidelines based on individual patient's circumstances.

The strengths of this study include two homogeneous cohorts of patients that are larger than those used in previous studies examining TA dosing. Furthermore, this study compared two TA dosing protocols that are within the range of contemporary clinical practice.

## CONCLUSION

The current investigation suggests that a low-dose protocol of TA for patients undergoing primary CABG surgery via sternotomy with CPB is equivalent to a high-dose strategy for the outcomes of post-operative chest tube output and perioperative transfusion requirements. Furthermore, this low-dose protocol may help to avoid side effects of TA such as convulsions that are associated with higher TA doses and accumulation of TA in susceptible individuals.

### Acknowledgement

This project described here was supported by the National Institute of Health through Grant number UL1-TR-000005.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, *et al.* Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006;34:1608-16.
2. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, *et al.* Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg 2006;81:1650-7.
3. Divatia J. Blood transfusion in anaesthesia and critical care: Less is more! Indian J Anaesth 2014;58:511-4.
4. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, *et al.* A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319-31.
5. Horrow JC, Van Riper DF, Strong MD, Grunewald KE, Parmet JL. The dose-response relationship of tranexamic acid. Anesthesiology 1995;82:383-92.
6. Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, Dagenais F. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. Ann Thorac Surg 2012;93:148-54.
7. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure – Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12.
8. Stover EP, Siegel LC, Parks R, Levin J, Body SC, Maddi R, *et al.* Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: A 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. Anesthesiology 1998;88:327-33.
9. Surgenor SD, DeFoe GR, Fillinger MP, Likosky DS, Groom RC, Clark C, *et al.* Intraoperative red blood cell transfusion during coronary artery bypass graft surgery increases the risk of postoperative low-output heart failure. Circulation 2006;114 1 Suppl: I43-8.
10. Brown RS, Thwaites BK, Mongan PD. Tranexamic acid is effective in decreasing postoperative bleeding and transfusions in primary coronary artery bypass operations: A double-blind, randomized, placebo-controlled trial. Anesth Analg 1997;85:963-70.
11. Santos AT, Kalil RA, Bauemann C, Pereira JB, Nesralla IA. A randomized, double-blind, and placebo-controlled study with tranexamic acid of bleeding and fibrinolytic activity after primary coronary artery bypass grafting. Braz J Med Biol Res 2006;39:63-9.
12. Shi J, Wang G, Lv H, Yuan S, Wang Y, Ji H, *et al.* Tranexamic acid in on-pump coronary artery bypass grafting without

clopidogrel and aspirin cessation: Randomized trial and 1-year follow-up. Ann Thorac Surg 2013;95:795-802.
13. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011;1:CD001886.
14. Waldow T, Szlapka M, Haferkorn M, Bürger L, Plötze K, Matschke K. Prospective clinical trial on dosage optimizing of tranexamic acid in non-emergency cardiac surgery procedures. Clin Hemorheol Microcirc 2013;55:457-68.
15. Karski JM, Dowd NP, Joiner R, Carroll J, Peniston C, Bailey K, *et al.* The effect of three different doses of tranexamic acid on blood loss after cardiac surgery with mild systemic hypothermia (32 degrees C). J Cardiothorac Vasc Anesth 1998;12:642-6.
16. Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol Suppl (R Coll Pathol) 1980;14:41-7.
17. Sigaut S, Tremey B, Ouattara A, Couturier R, Taberlet C, Grassin-Delyle S, *et al.* Comparison of two doses of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology 2014;120:590-600.
18. Dowd NP, Karski JM, Cheng DC, Carroll JA, Lin Y, James RL, *et al.* Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. Anesthesiology 2002;97:390-9.
19. Fiechtner BK, Nuttall GA, Johnson ME, Dong Y, Sujirattanawimol N, Oliver WC Jr., *et al.* Plasma tranexamic acid concentrations during cardiopulmonary bypass. Anesth Analg 2001;92:1131-6.
20. Nuttall GA, Gutierrez MC, Dewey JD, Johnson ME, Oyen LJ, Hanson AC, *et al.* A preliminary study of a new tranexamic acid dosing schedule for cardiac surgery. J Cardiothorac Vasc Anesth 2008;22:230-5.
21. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg 2010;110:350-3.
22. Manji RA, Grocott HP, Leake J, Ariano RE, Manji JS, Menkis AH, *et al.* Seizures following cardiac surgery: The impact of tranexamic acid and other risk factors. Can J Anaesth 2012;59:6-13.
23. Keyl C, Uhl R, Beyersdorf F, Stampf S, Lehane C, Wiesenack C, *et al.* High-dose tranexamic acid is related to increased risk of generalized seizures after aortic valve replacement. Eur J Cardiothorac Surg 2011;39:e114-21.
24. Montes FR, Pardo DF, Carreño M, Arciniegas C, Dennis RJ, Umaña JP. Risk factors associated with postoperative seizures in patients undergoing cardiac surgery who received tranexamic acid: A case-control study. Ann Card Anaesth 2012;15:6-12.
25. Goldstone AB, Bronster DJ, Anyanwu AC, Goldstein MA, Filsoufi F, Adams DH, *et al.* Predictors and outcomes of seizures after cardiac surgery: A multivariable analysis of 2,578 patients. Ann Thorac Surg 2011;91:514-8.
26. Furtmüller R, Schlag MG, Berger M, Hopf R, Huck S, Sieghart W, *et al.* Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by a gamma-aminobutyric acid(A) receptor antagonistic effect. J Pharmacol Exp Ther 2002;301:168-73.
27. Mohseni K, Jafari A, Nobahar MR, Arami A. Polymyoclonus seizure resulting from accidental injection of tranexamic acid in spinal anesthesia. Anesth Analg 2009;108:1984-6.
28. Yeh HM, Lau HP, Lin PL, Sun WZ, Mok MS. Convulsions and refractory ventricular fibrillation after intrathecal injection of a massive dose of tranexamic acid. Anesthesiology 2003;98:270-2.
29. Garg J, Pinnamaneni S, Aronow WS, Ahmad H. ST elevation myocardial infarction after tranexamic acid: First reported case in the United States. Am J Ther 2014;21:e221-4.
30. Mandal AK, Missouris CG. Tranexamic acid and acute myocardial infarction. Br J Cardiol 2005;12:306-7.