

Original Article

Effect of Perioperative Administration of Tranexamic Acid on Postoperative Bleeding Following on Pump CABG

A Y M Shahidullah¹, A M Asif Rahim², A S M Iftekher Hossain², Syed Monirul Islam³,
Md Sajedul Bari⁴, Nazmul Hosain²

¹Department of Cardiac Surgery, AFC health-Fortis Escorts Heart Institute, Khulna, ²Department of Cardiac Surgery, Chittagong Medical College, Chittagong, ³Department of Cardiac Surgery, Sir Salimullah Medical College, Dhaka, ⁴Department of Cardiac Surgery, NICVD, Dhaka

Abstract

Key Words :
CABG, IHD
Tranexamic acid,
Postoperative
bleeding.

Background: One of the main causes of post-operative morbidity in cardiac surgical patient is excessive bleeding requiring transfusion of blood component after CPB. Re-exploration due to bleeding occurs in 2% to 7% of post bypass patient and 50% to 80% of these patients not having any identifiable surgical bleeding source. Tranexamic acid is competitive inhibitor of plasminogen activator and at higher concentration a non-competitive inhibitor of plasmin. It is 10 times more potent than Epsilone Aminocaproic Acid in preventing post-operative haemorrhage following CPB.

Methods: This study was conducted in the Department of Cardiac Surgery, National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh between January 2009 and December 2010. The Study population was divided into two groups. Group A comprised of 35 patients, who had received Tranexamic Acid 10 mg /kg after induction and then 1 mg/kg/hour till time of protamin infusion and Group B comprised of 35 patients who had received same amount of normal saline 0.9% NaCl as placebo.

Results: The postoperative bleeding during both 1 to 4 hours and 4 to 24 hours was significantly lower in the Tranexamic Acid group as compared to the placebo group (p value <0.001). There was no significant difference between groups in terms of platelet count and prothrombin time.

Conclusion: From the study, we conclude that "Perioperative Administration of Tranexamic acid reduces post operative bleeding and also reduces the need for postoperative blood transfusion in CABG patents using Cardiopulmonary bypass". Therefore it is recommended that routine prophylactic use of Tranexamic Acid should be carried out to decrease the postoperative hemorrhage and requirement blood transfusion.

(*Cardiovasc. j.* 2019; 12(1): 20-23)

Introduction:

Coronary artery bypass grafting (CABG) has become the standard operative treatment of ischemic heart disease. One of the main causes of post operative morbidity in cardiac surgical patient is excessive bleeding requiring transfusion of blood component after CPB. Use of cardiopulmonary bypass during cardiac surgical procedures causes a significant disruption of coagulation system. In addition to haemodilution from a crystalloid prime, contact of

blood with the extracorporeal circuit activates platelets & several cascades that activate the extrinsic and intrinsic coagulation system and trigger fibrinolysis. Thrombin generation leads to generalized fibrinolysis during and after CPB, with deleterious effect on platelet function. Increased fibrinolytic activity and platelet dysfunction are important cause of post-operative bleeding. Antifibrinolytic drugs are used to prevent platelet dysfunction and decrease perioperative bleeding.¹

Address of Correspondence: Dr. A Y M Shahidullah, Department of Cardiac Surgery, AFC health-Fortis Escorts Heart Institute, Khulna, Bangladesh.

© 2018 authors; licensed and published by International Society of Cardiovascular Ultrasound, Bangladesh Chapter and Bangladesh Society of Geriatric Cardiology. This is an Open Access article distributed under the terms of the CC BY NC 4.0 (<https://creativecommons.org/licenses/by-nc/4.0>).

Significant post bypass bleeding is reported in 6% to 25% of open heart patient post operatively. Fibrinolysis can be detected in 50% of post bypass patient and has been reported to be the cause of 25% to 45% of significant post bypass bleeding. Re-exploration due to bleeding occurs in 2% to 7% of post bypass patient and 50% to 80% of these patients with not having identifiable surgical bleeding source.²

Various pharmacological agents have been used to diminish post by pass bleeding including Prostacyclin, Desmopressin, Aprotinine, Epsilone Aminocaproic Acid (EACA) and Tranexamic acid (TA). Ali³ showed in his study “Comparative study in between Tranexamic acid and Epsilone Aminocaproic Acid (EACA) in preventing postoperative haemorrhage following CPB in open heart surgery” that the amount of total transfusion was 1090.5 ± 61.7 ml.

TA is competitive inhibitor of plasminogen activator and at higher concentration a non- competitive inhibitor of plasmin. It is 10 times more potent than EACA. Tranexamic acid excreted largely unchanged in urine.

Methods:

This study was conducted in the department of cardiac surgery, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh between January 2009 and December 2010. The study was carried out on patients admitted for coronary artery bypass graft surgery (CABG). Exclusion criteria were Ejection Fraction <30%, Renal failure, Hepatic failure, history of abnormal bleeding, previous history of stroke, H/O taking anti-platelet drugs within 7 days of operation, peripheral vascular disease, CCF, recent MI, perioperative use of IABP, previous history of cardiac surgery and known allergy to Tranexamic Acid. The Study population was divided into two groups. Group A comprised of 35 patients who had received Tranexamic Acid 10 mg /kg after induction and then 1 mg/kg/hour till time of protamin infusion. Group B comprised of 35 patients who had received normal saline 0.9% NaCl as placebo.

Patients admitted in the department of cardiac surgery NICVD, fulfilling the inclusion criteria & exclusion criteria were considered for the study. The decision for a patient to undergo operation whether

conventional or on pump beating heart technique was decided by the operating surgeon. Patients were fully heparinized with 3-4 mg/kg to achieve an Activated Clotting Time of 450 sec or more. Heparin neutralization was done by protamine in 1:1 ratio at the end of procedure. Hemodynamic parameters were monitored by invasive & non-invasive method throughout the procedure. Tranexamic Acid was given in group-A patients 10 mg /kg after induction and before incision and then 1 mg/kg/hour till time of protamin infusion. Normal saline (NaCl) was given in group-B patients instead of TA. The standard CPB circuit incorporated a roller pump (3M Sarns™, USA) and a hollow-fiber membrane oxygenator (Affinity® NT, Medtronic Inc., USA).

On completion of surgery, patients were transferred to ICU where they were under invasive & non-invasive hemodynamic monitoring and elective ventilation until ready for extubation. Post operatively patients were assed for amount of bleeding at the end of 4 hour and 24 hour. The total amount was recorded till drain tube removed. Total amount of transfused unit of blood were also recorded at the end of 24 hour.

Data were collected by use of interview schedule, investigation and from hospital records and was put in a pre-designed questionnaire and then entered into a computer and data file was constructed. The numerical data obtained from the study were analyzed and significance of difference was estimated by using the statistical methods. All data were analyzed by using computer based Statistical Programs for Social Science (SPSS) program, Version 12 (SPSS Inc., Chicago, IL, USA). P value less than 0.05 was considered as significant.

Results :

Distribution of age, sex and NYHA functional class between Tranexamic Acid and placebo groups was identical. The preoperative coagulation profile shows that the hematocrit value, platelet count, prothrombin time and clotting time were almost identical between Tranexamic Acid and placebo group. In terms of the mean ECCT, X-clamp time and total operative time difference between groups were not significant. Around two-thirds of the patients in each group received 3 grafts and rest one-third 2 grafts ($p = 0.600$).

Table-I
Comparison of postoperative bleeding between two groups.

Postoperative bleeding	Group		p-value
	Tranexamic Acid(n = 35)	Placebo(n = 35)	
1 st 4 hrs	214.3 ± 9.8	277.0 ± 7.4	<0.001
4 – 24 hrs	241.7 ± 10.4	352.0 ± 14.6	<0.001
Total bleeding	549.5 ± 25.7	806.7 ± 24.0	<0.001

The postoperative bleeding during both 1 to 4 hours and 4 to 24 hours was significantly lower in the Tranexamic Acid group as compared to the placebo group (P value <0.001) as shown in Table I. The total postoperative bleeding was also significantly lower in the Tranexamic Acid group. However, there was no significant difference between groups in terms of platelet count during the same time frame (p = 0.201 and p = 0.468 respectively) as shown in Fig 1. The mean difference in prothrombin time between Tranexamic Acid and Placebo groups following operation was negligible as evident by the data presented in table VIII & Fig. 6 (p = 0.617 and p = 0.387).

The mean plasma D-dimer at 4 and 12 – 24 hours were significantly less in the Tranexamic Acid group than those in the placebo group (387.1 ± 15.5 vs. 605.2 ± 17.8 ng/ml, p < 0.001 and 324.6 ± 13.6 vs. 491.7 ± 14.9 ng/ml, p < 0.001 respectively).

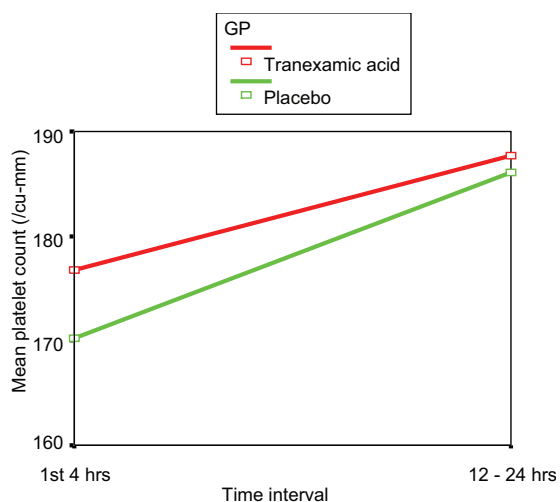


Fig.-1: *Changes in platelet count at different time intervals.*

Only two patients needed fresh frozen plasma transfusion, one on each group. No patient needed Platelet transfusion. This study revealed that the

amount of fresh frozen plasma transfused in each group was not significant (p = 0.5).

One patient on each group needed reopening for bleeding (p=0.5). Tranexamic acid group patient bled from a side branch of venous graft which was ligated. Placebo group patient had a surgical bleeding source from LIMA bed which was clipped. No patient on both groups had developed MI, pulmonary thromboembolism, DVT or stroke.

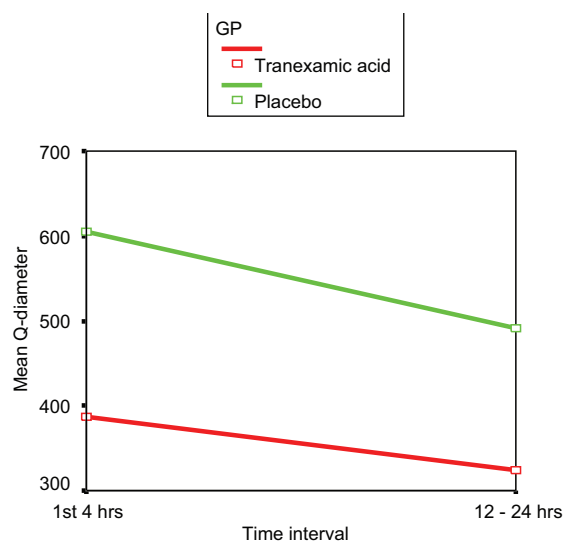


Fig.-2: *Changes D-dimer at different time intervals.*

Discussion:

National Institute of Cardiovascular Disease, Dhaka, Bangladesh has been performing the central role in the field of cardiac surgery. NICVD is one of the major referral hospitals for CABG operations. The first on pump CABG surgery was performed at NICVD in 1985.

Preoperative patient characteristics and cardiopulmonary functional status were similar in both the study groups. In this study post-operative platelet counts were not significantly different

between the two groups both at 4 hour and 24 hour after operation ($p = 0.201$ and 0.468 respectively) which was similar to the findings of Maddali,¹ and Zabeeda.⁴ Postoperative Prothrombin time were also similar in both groups at 4th and 24th hours similar to the findings of Katsaros⁵ and Maddali.¹ Activated Partial Thromboplastin Time (aPTT) were comparable in both groups during the same period ($p = 0.105$ and $p = 0.129$ respectively) similar to the findings of Brown,⁶ Andreasen⁷ and Santos.^{8,10,11}

Fibrinolysis has long been considered to be an important factor of post-operative bleeding. The lower plasma D-dimer levels in the TA groups confirm that TA inhibited fibrinolysis, especially since D-dimer concentration is a sensitive quantitative measure of fibrinolysis. Postoperative D-dimer at 4 hour and 24 hours after operation were significantly lower in Tranexamic group ($p < 0.001$ and $p < 0.001$ respectively) similar to the findings of Andreasen⁷ and Pleym.⁹

There were significant differences in Post-operative bleeding. The total amount of bleeding following operation was observed to be significantly less ($p < 0.001$) in the Tranexamic acid group than that in the placebo group similar to the findings of Santos,⁸ Andreasen⁷ and Zabeeda.³ Regarding post-operative complication one patient on each group needed reoperation for bleeding ($p=0.5$). Tranexamic acid group patient bled from a side branch of venous graft which was ligated. Placebo group patient had a surgical bleeding source from LIMA bed which was clipped. No patient on both groups had developed MI, pulmonary thromboembolism, DVT or stroke.

Ali³ reported study in NICVD with two patients in EACA group reoperated for bleeding, as opposed to none in TA group. Regarding wound infection there were one patient in TA group and five patients in EACA group. One patient from each group developed renal impairment. Two patients in TA group and three patients in EACA group developed pulmonary dysfunction. Zabeeda⁴ reported study with two patients was re-explored for bleeding for surgical cause, one each in TA group and placebo group. There was no electrocardiographic evidence of MI, no gross neurological events i.e., stroke and no mediastinal infection.

Conclusion:

Perioperative Administration of Tranexamic acid reduces post-operative bleeding and the need for postoperative blood transfusion in CABG patients using Cardiopulmonary bypass. Routine

prophylactic use of Tranexamic Acid can decrease requirement postoperative blood transfusion. A prospective randomized trial with bigger study population and long time follow-up is recommended to confirm our findings.

Conflict of Interest - None.

References:

1. Madalli MM, Rajakumar MC. Tranexamic Acid and Primary Coronary Artery Bypass Surgery: a Prospective Study. *Asian Cardiovascular & Thoracic Annals*;15 (4): 313-319.
2. Casati V, Gerli C, Franco A, Torri G, D2 Angelo A, Benussi S, et al. Tranexamic Acid in Off- Pump Coronary Surgery: A Preliminary, Randomized, Double-Blind, Placebo-Controlled Study. *Annals of Thoracic Surgery* 2001; 72: 470-475.
3. Ali S. *Comparative Study in between Tranexamic Acid and epsilon Aminocaproic Acid in preventing postoperative haemorrhage following Cardiopulmonary Bypass in Open Heart Surgery*. MS. Dhaka: University of Dhaka.
4. Zabeeda D, Medalion B, Sverdlov M, Erza S, Scharchner A, Ezri T, et al. Tranexamic Acid reduces bleeding the need for blood transfusion in Primary Myocardial Revascularization. *Annals of Thoracic Surgery* 2002; 74:733-738.
5. Katsaros D, Petricevic M, Snow NJ, Woodhall DD, Bergen RV. Tranexamic Acid Reduces Post Bypass Blood Use: A Double Blinded, Prospective, Randomized Study of 210 Patients. *Annals of Thoracic Surgery* 1996; 61:1131-1135.
6. Brown RS, Thwaites BK, Mongan PD. Tranexamic Acid is effective in Decreasing Post Operative Bleeding and Transfusions in Primary Coronary Artery Bypass Operations: A Double Blind, Randomized, Placebo Controlled Trial. *Anesthesia and Analgesia* 1997; 85: 963-970.
7. Andreasen JJ, Nielsen C. Prophylactic Tranexamic Acid in elective primary coronary artery btpass surgery using cardiopulmonary bypass. *Eur J Cardiothorac Surg* 2004; 26: 311-317.
8. Santos ATL, Kalil RAK, Bauemann C, Pareira 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: 63-69.
9. Pleym H, Stenseth R, Wahba A, Bjella L, Karevold A, Dale O. Single Dose Tranexamic Acid Reduces Postoperative Bleeding After Coronary Artery Surgery in Patients Treated with Aspirin Until Surgery. *Cardiovascular Anaesthesia* 2003; 96:923-928.