

COMPARISON OF DIFFERENT DOSES OF TRANEXAMIC ACID ON POST-OPERATIVE BLEEDING IN PATIENTS OF CABG SURGERY

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ABSTRACT

Objective: To compare three different dosing schedules of tranexamic acid to achieve good hemostasis intra-operatively and in post-operative period.

Design: Randomized controlled trials.

Place and Duration of Study: Anaesthesia department, Armed Forces Institute of Cardiology/National Institute of Heart Diseases (June 2011 to Jan 2013)

Patients and Methods: A total of 128 patients, due for coronary artery bypass grafting were included in this study after informed consent. The patients were randomly divided into four groups. Group A, being the control group, did not receive tranexamic acid during the operation, whereas the remaining three groups received tranexamic acid just after the reversal of heparin with protamine sulphate. Group B received low dose, group C received medium dose and group D received high dose of tranexamic acid both as bolus and followed by infusion. Six patients, 4 from group B and 2 from group D were dropped out due to incomplete data or some complication. The blood loss at 6 hours and 24 hours after surgery were noted along with amount and type of transfusions needed and clinical outcomes. The total cardio-pulmonary bypass time, aortic cross-clamp time and chest closure time were also noted. Haemoglobin levels, coagulation profile and activated clotting time were noted and compared pre and post operatively.

Results: All the 4 groups were comparable with respect to age, weight, gender and personal history. Average bleeding in group A was similar to group B after six hours ($p = 0.755$) and 24 hours ($p = 0.343$) but significantly higher as compared to group C ($p < 0.001$) and group D ($p < 0.001$). Group B also had more blood in chest drain as compared to group C ($p < 0.001$) and group D ($p < 0.001$). Group C and group D had almost similar amount of blood loss after 6 hours ($p = 0.916$) as well as after 24 hours ($p = 0.834$).

Conclusion: This study showed that tranexamic acid, when given at a loading dose of 20 mg/kg or greater and followed by a maintenance infusion of 15 mg/kg/hr or greater, significantly reduced the amount of blood loss, both intra-operatively and post-operatively, in patients undergoing on-pump coronary artery bypass grafting.

Keywords: Cardiopulmonary bypass, Coronary artery bypass grafting, Tranexamic acid,.

INTRODUCTION

Post-operative bleeding following coronary artery bypass surgery (CABG) on cardio-pulmonary bypass (CPB) may lead to allogeneic blood transfusions and/or reoperation, which are independently associated with a number of detrimental effects on patient outcome^{1,2}.

Various causes of post operative bleeding have been pointed out. Most common are defective surgical hemostasis and acquired platelet dysfunction³. Thrombin generation

occurs during CPB despite systemic heparinization⁴. This leads to generalized fibrinolysis during and immediately after CPB, with deleterious effects on platelet function. Increased fibrinolytic activity along with platelet dysfunction leads to postoperative bleeding. More uncommonly, thrombocytopenia, vitamin K dependent factor deficiencies, coagulopathy, and heparin rebound may lead to post-operative bleeding⁵.

Although attempts to modify the degree of post-operative bleeding with pharmacologic therapy have met limited success, anti-fibrinolytics are widely used in cardiac surgery to prevent platelet dysfunction and decrease perioperative bleeding⁶⁻⁸. The withdrawal of

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marketing approval for aprotinin resulted in more clinicians administering tranexamic acid (TA) to patients at increased risk of bleeding and adverse outcome⁹.

Tranexamic acid (TA) is useful in a wide variety of haemorrhagic conditions¹⁰. This synthetic anti-fibrinolytic drug acts by forming a reversible complex with plasminogen and plasmin through the lysine-binding sites, blocking interaction with the specific lysine residues of fibrin⁶. This retards fibrinolysis because although plasmin is still formed, it is unable to bind to fibrin. Tranexamic acid also preserves platelet function by reducing the effect of plasmin on platelet glycoprotein 1b receptors.

The primary objective of the present study was to determine the most effective dose of TA required to reduce post operative bleeding thus reducing the proportion of patients requiring perioperative transfusions while undergoing primary, elective CABG using cardiopulmonary bypass.

PATIENTS AND METHODS

These randomized controlled trials were carried out at Armed Forces Institute of Cardiology (AFIC) / National Institute of Heart Diseases (NIHD) Rawalpindi, after approval from ethical committee. One hundred and twenty eight patients were included in the study and written informed consent was taken from the patients in preoperative period. Patients who had deranged coagulation, history of bleeding diathesis, known clotting factor deficiencies, emergency CABG, redo cardiac surgery, patients who were reopened due to excess bleeding and found to have surgical bleed and undergoing concomitant valvular surgery with CABG were excluded. Further exclusion criteria comprised of patients who were on anticoagulants like warfarin, patients taking aspirin within last 7 days, having intra-aortic ballon pump (IABP) perioperatively, liver or renal dysfunction, pregnant women, patients suffering from tumours of any origin, anemia with hematocrit < 33% preoperatively, platelet count < 100000 and

due to any reason when the anticoagulants had to be started post-operatively (for e.g., bad target vessels, end-arterectomy of the target vessels or perioperative myocardial infarction etc).

Drug was prepared by a nursing assistant who was not directly involved in the patient treatment and secrecy was maintained at all levels that only the person who prepared the injection knew about the drug dose.

Group A was the control group and did not receive TA at any stage during the study. The remaining three groups were given TA in varying doses. Group B received 10 mg/kg IV bolus of TA and 10 mg/kg/hr as IV infusion. Group C received the drug at 20 mg/kg IV bolus followed by IV infusion of 15 mg/kg/hr. Group D was administered TA at the rate of 30 mg/kg IV bolus followed by 20 mg/kg/hr IV infusion. The IV bolus of TA was given over 20 minutes just after reversal of heparin with protamine sulphate followed by infusion for first six hours postoperatively.

The anesthesia protocol comprised of induction with intravenous midazolam, fentanyl or nalbuphine and atracurium in doses according to body weight. Anesthesia was maintained with isoflurane, propofol, fentanyl or nalbuphine and atracurium infusions with standard monitoring of pulse oximetry, invasive arterial pressure monitoring, 7 lead ECG with ST analysis, end tidal carbon dioxide monitoring, skin and nasopharyngeal temperature probes and hourly urine output.

Before CPB, systemic heparinization was carried out with unfractionated heparin at initial dose of 300 I.U / kg. An activated clotting time of > 400 seconds was targeted; additional 100 I.U /kg were given if required. Afterwards the heparin was reversed with protamine sulphate at the initial dosage of 3 mg/kg. Activated clotting time was measured before and after heparin administration, every 30 minutes during cardiopulmonary bypass, after protamine administration and immediately after reaching the post-surgical ICU. Before separation from

cardiopulmonary bypass the patient was rewarmed to 37°C and normothermia was maintained throughout the post-surgical period. The blood loss was recorded in the chest drain bottle at 6 hours and 24 hours of the start of

Table-1: Criteria for blood and blood products transfusion.

Blood product	Indication / transfusion trigger
Red cell concentrate	If HCT < 26%(young patients with good LV functions) and HCT < 30% (age > 65 and moderately impaired LV functions), Chest drainage > 250 ml/hour, signs of hypervolemia with gradually lowering of hematocrit.
Platelets	Platelet count less than 100,000 with chest drain 250 ml/hour
Fresh frozen plasma	Prolonged PT and PTTK (> 1.5 times the control) with no sign of clot formation with chest drain > 300 ml/hour and INR > 1.5.

Table-2: Comparison of personal history between the groups.

	Group A (n = 32)	Group B (n = 28)	Group C (n = 32)	Group D (n = 30)	p-value
Gender (Male)	29 (90.6%)	24 (85.7%)	27 (84.4%)	27 (90%)	0.842
Diabetics	10 (31.3%)	10 (35.7%)	15 (46.9%)	12 (40%)	0.620
Hypertensive	12 (37.5%)	9 (32.1%)	13 (40.6%)	4 (13.3%)	0.094
Smokers	9 (28.1%)	4 (14.3%)	5 (15.6%)	5 (16.7%)	0.477

Table-3: Comparison of blood loss in chest drain at 6 hours and 24 hours between the groups.

Drain	Group A (n = 32)	Group B (n = 28)	Group C (n = 32)	Group D (n = 30)	p-value
At 6 hours					
Mean ± SE	363.13 ± 42.50	326.96 ± 40.26	154.69 ± 62.73	158.17 ± 62.62	< 0.001
Median (IQ Range)	270 (180 – 550)	290 (180 – 397)	173 (112 – 190)	160 (115 – 205)	
At 24 hours					
Mean ± SE	733.81 ± 76.01	644.29 ± 70	294.38 ± 16.87	294.79 ± 22.19	< 0.001
Median (IQ Range)	625 (452–1087)	555 (410–766.2)	298.5 (242.5-35)	290 (189.5–370)	

maintained throughout the post-surgical period. The cell savers were not used in perioperative period.

tranexamic acid infusion on the study proforma. The blood and blood product transfusion including red cell concentrates, platelets and fresh frozen plasma were carried out according to

the criteria described in table 1 during the first 24 hours postoperatively and were recorded on 8.85), in group B it was 55.21 years (SD = 7.81), in group C it was 55.91 years (SD = 9.54) and in

Table-4: Comparison of peri-operative variables between the groups.

	Group A (n = 32)	Group B (n = 28)	Group C (n = 32)	Group D (n = 30)	p-value
CPB time	107.5 ± 14.17	118.5 ± 12.9	86.1 ± 6.9	91 ± 6.5	0.330
Xclamp time	63.8 ± 9	69.6 ± 7.6	47.8 ± 4.2	53.4 ± 4.5	0.178
Chest closure time	58.8 ± 2.8	59 ± 2.5	49.3 ± 1.9*¶	48.3 ± 9.5*¶	< 0.001
ACT control	100.5 ± 3.6	99.6 ± 4.5	99.2 ± 2.7	91.5 ± 2.8	0.221
ACT post protamine	118.3 ± 4.1	111.6 ± 2.9	111.3 ± 2.6	118 ± 5.5	0.519
Pre Hb	13.6 ± 0.26	13 ± 0.28	13.4 ± 0.28	13.7 ± 0.28	0.287
Post Hb	10.5 ± 0.28	9.9 ± 0.32	11 ± 0.25¶	10.6 ± 0.26	0.042

* = significantly different from group A . ¶ = significantly different from group B

study proforma. Six patients, 4 from group B and 2 patients from group D were dropped out due to incomplete data or some complication.

Statistical Analysis

Data was analyzed using SPSS version 17. Descriptive statistics were used to describe the results i.e. mean, standard deviation (SD), median and interquartile range for quantitative variables while frequency and percentage for qualitative variables. Chi-square test was applied for the comparison of qualitative variables while analysis of variance (ANOVA) or Kruskal-Wallis H test was used for the comparison of quantitative variables where appropriate. A *p*-value < 0.05 was considered significant.

RESULTS

Total 128 patients were included in the study and were randomly divided into four groups of 32 each. Four patients from group B and 2 patients from group D were dropped out. Average age in group A was 56.25 years (SD =

group D it was 54.33 years (SD = 8.42). Average weight in group A was 69.47 kg (SD = 11.51), in group B it was 72.54 kg (SD = 9.37), in group C it was 72.25 kg (SD = 9.40) and in group D it was 73.93 kg (SD = 9.64). All the groups were comparable with respect to age (*p* = 0.832) and weight (*p* = 0.360). All the groups were also comparable with respect to gender and personal history (table-2).

Average blood loss in group A was similar to group B after six hours (*p* = 0.755) and 24 hours (*p* = 0.343) but significantly higher as compared to group C (*p* < 0.001) and group D (*p* < 0.001). Group B also had higher blood loss in chest drain as compared to group C (*p* < 0.001) and group D (*p* < 0.001). Group C and D had almost similar amount of blood loss after 6 hours (*p* = 0.916) as well as after 24 hours (*p* = 0.834). (Table-3)

Comparison of peri-operative variables is shown in table-4. The quantity of red cell concentrate transfused was significantly lower in

group C and D as compared to groups A and B ($p < 0.001$). ICU stay was significantly higher in groups A and B as compared to groups C and D ($p < 0.001$).

DISCUSSION

Our institute is a tertiary cardiac care center in Pakistan where several surgeons at various stages of expertise and training are performing CABG surgery. The different levels of expertise can be one of the reasons for high postoperative blood loss and transfusion requirements.

The efficacy of all anti-fibrinolytics in cardiac surgery has been established, but comparative data is inconclusive to suggest an agent of choice¹¹. The extensively studied anti-fibrinolytic aprotinin is efficacious, but its continuous use is associated with serious end organ damage¹². The Food and Drug Administration issued a Public Health Advisory on February, 2006, that aprotinin has been linked to serious side effects including renal problems, myocardial events and strokes in patients undergoing CABG. Neither of the alternative anti-fibrinolytics including epsilon, aminocaproic acid (EACA) and TA has been shown to be associated with such effects. Among these three drugs, TA has the greatest efficacy, a longer half-life, a stronger plasminogen binding and a more sustained anti-fibrinolytic effect. It also has the additional advantage of being inexpensive and easy to stock and handle^{13,14}.

A review of multiple studies shows that different dosage regimens of TA have been used in cardiac surgery but the ideal dosage of TA remains controversial¹⁵⁻¹⁹. The use of bolus dose followed by a maintenance infusion deals with the fast metabolism of TA, half-life being 80 min and prolongs the efficacy. Fiechtner and colleagues reported that the dosing regimen of bolus dose followed by infusion of TA results in adequate plasma concentrations to prevent fibrinolysis, with relatively stable levels throughout CPB²⁰. Another study showed that the use of TA during coronary artery bypass grafting significantly reduced the coagulopathy-

induced postoperative bleeding and allogeneic blood products requirement²¹.

We administered the IV bolus of TA just after reversal of heparin with protamine sulphate over 20 minutes followed by infusion for first six hours post-operatively. We demonstrated that the patients with TA with a bolus dose of 20 mg/kg or greater had significantly less post-operative bleeding and lesser need for blood and blood products compared to those who received a low dose of TA or a placebo. Since same team of surgeons with various skill levels were involved in all groups, we therefore deduce that TA was responsible for reduced post-operative bleeding. These results were supported by other studies that demonstrated the efficacy of TA in reducing blood loss after primary cardiac surgery^{7,22,23}.

Multiple factors have been attributed to effect chest closure time like hemodynamic stability, quality of bone and expertise of surgeons. Since in all groups included in our study, these confounding factors were similar therefore we took chest closure time as an indicator of hemostasis. Our results indicated that chest closure time was significantly reduced in group C and D as compared to control and group A. Thus the shorter closure time indicated faster hemostasis.

In our study, we also demonstrated that the requirement of blood transfusions was also significantly low in groups receiving medium and high doses of TA as compared to control and low dose groups. This finding also supports that the fact that TA reduces blood loss and appears to be an effective treatment for patients undergoing on-pump CABG surgery^{24,25}.

CONCLUSION

Tranexamic acid in a dose of 20 mg/kg as a bolus followed by 15 mg/kg/hr for first 6 hours post-operatively, used in patients undergoing CABG with CPB is effective in reducing postoperative blood loss and the need for allogeneic blood transfusions. Reduction in chest closure time supports earlier surgical hemostasis.

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