ORIGINAL ARTICLE

EFFECTS OF BOLUS DOSE AND CONTINUOUS INFUSION OF TRANEXAMIC ACID ON BLOOD LOSS AFTER CORONARY ARTERY BYPASS GRAFTING

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Background: Cardiac surgery is associated with excessive bleeding that is as a result of coagulopathy caused by cardiopulmonary bypass. We evaluated the effect of two different modalities for administering similar doses of tranexamic acid on bleeding following primary elective coronary artery bypass grafting (CABG). **Methods:** In the randomized control trial. 137 patients scheduled for CABG were randomized to two groups applying different modalities of tranexamic acid administration (bolus injection of 30 mg/kg vs. continuous infusion). Blood loss until removal of chest tubes was the primary outcome measure; we also recorded and assessed blood products transfused, and length of ICU stay. **Results:** Both the groups were comparable at baseline. Trends toward transfusion differences between groups were not statistically significant. No differences in length of ICU stay, morbidity or mortality were found. **Conclusion:** In CABG surgery, the use of either method for administering similar doses of tranexamic acid leads to a similarl reduction in postoperative mediastinal bleeding.

Keywords: Tranexamic acid, CABG, cardiac surgery, antifibrinolytic

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INTRODUCTION

Cardiac surgery is associated with excessive bleeding that is 5–25%[1] as a result of coagulopathy caused by cardiopulmonary bypass (CPB) and requires transfusions; this not only represents a major burden on blood banking organizations at all levels, but also constitutes a risk for each patient receiving allogeneic blood products. The coagulopathy is multifactorial with platelet dysfunction and plasmin induced fibrinolytic activity the major contributors.[2] Prophylactic use of antifibrinolytic drugs to minimize postoperative blood loses and transfusion of blood products has been advocated so that the risk of transmitting serious viral infections and complications such as renal failure, sepsis, arrhythmias, prolonged requirement for mechanical ventilation, longer hospital stay and mortality can be reduced.[2–5]

Most of the work in cardiac surgery has been done on blood sparing effects of aprotinin a serine protease inhibitor from bovine lung.[6-9] This agent reduces blood loss and transfusions after CPB but it may sensitize patients and may be associated with worsening myocardial, cerebrovascular and renal function.[6] Aprotinin was approved antifibrinolytic agent by FDA in high risk cardiac surgery but its use is associated increased mortality and morbidity as compared to tranexamic acid[7] so FDA limited its but no restriction on tranexamic acid use.[8]

Other antifibrinolytic agent is tranexamic acid which is very much cheaper and equally effective as aprotinin in reducing bleeding and the use of allogeneic blood products in cardiac surgery.[9,10] Several studies and meta analyses have shown a reduction in postoperative bleeding and transfusion requirements of this antifibrinolytic drug.[11] But no trial has been done to compare the two modes of administration of this drug in randomized controlled design in coronary artery bypass grafting (CABG).

Tranexamic acid is a cheap synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockage of lysine-binding sites on plasminogen molecules, thereby inhibiting the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin.[12–14]

This study investigated the blood-saving effect of two different modalities for administering similar doses of tranexamic acid in a well-defined patient population. Only patients with a relatively low risk of excessive blood loss, undergoing first-time CABG were included. Our hypothesis was that infusion form of tranexamic acid is more effective as compared to bolus form in this patient population in reducing the incidence of perioperative blood loss and allogeneic blood transfusion.

MATERIAL AND METHODS

This randomized control trial was conducted at cardiac operation room and cardiac ICU of Rehman Medical Institute Hayatabad, Peshawar, a 300 bedded tertiary care teaching hospital. The study was approved by the institutional review board. All patients gave informed written consent.

Patients coming for elective primary CABG surgeries were included in study.

Exclusion criteria were Patients' refusal for participation in study; redo cardiac surgery, deep hypothermic circulatory arrest, urgent and emergency cardiac surgery, renal insufficiency serum creatinine level over 1.2 g/dl, history of hematologic disorders, hepatic dysfunction, and treatment with anticoagulants or nonsteroidal anti-inflammatory except aspirin.

Patients were assigned randomly to two groups (A) infusion group and (B) single-dose group using a research randomizing computer program.[15]

After heparin administration before CPB group-A received a bolus of 500 mg of tranexamic acid of calculated dose that is 30 mg/kg. Remaining dose was given in continuous infusion at 5mg/Kg/hour until the completion of dose.

Group B received a single bolus dose of 30 mg/kg of tranexamic acid after heparin administration before CPB in order to prevent thromboembolic events.

All patients received standard anesthetic induction using a combination of 0.2 mg/kg of etomidate, 5mg of midazolam, 0.3–0.5 mg/kg of morphine and 1–2% of isoflorane. Pancuronium at a dose of 0.1 mg/kg was used to facilitate orotracheal intubation. Intraoperative monitoring included five-lead electrocardiogram with continuous automated ST segment analysis, pulse oxymeter, capnogaram, a radial or brachial artery catheter to measure continuous arterial pressure and a central venous pressure line.

All operations were performed through median sternotomy with CPB using a semi occlusive roller pump and membrane oxygenator. Anticoagulation was achieved with 300 units/kg of 5% sodium heparin to maintain an activated clotting time above 450 seconds. The CPB circuit was primed with a total volume of 1450 mL, consisting of 500 mL of Ringer's lactate, 250 mL of 20% mannitol and 700 mL of colloids.

Synthetic colloids were added to the circuit as needed. Management of CPB included systemic temperature drift to 32–34 °C, targeted mean perfusion pressure between 50 and 70 mmHg, and pump flow rates of 2.2–3.0 L/min/m. Myocardial protection was achieved with an intermittent, ante grade or retrograde cold blood cardioplegia solution Surgical field blood was salvaged into the cardiotomy suction reservoir and returned through CPB circuit for as long as patients were anticoagulated. After weaning from CPB, heparin was neutralized with protamine sulfate in a dose of 1.2 mg for every 100 units of heparin to a targeted activated clotting time within 10% of baseline. Packed red blood cells were transfused to maintain the hematocrit value above 20% during CPB and at or above 25% after CPB. Other blood products were transfused according to standard clinical guidelines.[16]

All demographic, clinical and surgical data was recorded on standardized data collection forms. Intraoperative blood loss was not taken into consideration as it was very similar in all the patients. Post-operative blood loss until removal of mediastinal and pleural tubes was recorded, as well as transfusion of blood products during surgery and in the ICU. Haemoglobin and creatinine values were measured at two different times: preoperatively and upon discharge from the ICU. Intraoperative monitored data were minimum CPB temperature, CPB time, cross-clamp time, lowest hematocrit value on CPB. Intubation time and duration of ICU stay were also recorded.

Other clinical outcomes such as allergic reactions to tranexamic acid, incidence of perioperative myocardial infarction (new persistent Q-wave and increased troponin I values) were noted.

Sample size was calculated based on an estimated 24-h postoperative drainage loss of 600±350 mL, (Mean±SD) in both groups. A difference of 250 mL among groups was perceived as clinically relevant. A sample size of 50 patients per group would provide 80% power to detect this difference at α level of 0.025 with two-sided test of significance. Assuming a drop-out rate of 10%, the total sample size estimate was 140 patients, i.e., 70 patients in each group.

Data were analyzed using the SPSS-12. Normally distributed data were analyzed by Student's *t*-test or analysis of variance for repeated measures and reported as means±SD; 95% confidence intervals (CI) were calculated. Categorical data were analyzed by the $\chi 2$–test. A *p*-value less than 0.05 was considered being statistically significant.

RESULTS

One hundred and forty patients (70 in each treatment group) were randomized between January 2011 and May 2012. Two patients in group A and one in group B were withdrawn because intra-aortic balloon pump was inserted in these patients and heparin was given to prevent thromboembolism. Thus 137 patients completed the study according to protocol and were considered for statistical analysis.

There were no differences between two groups with respect to patient age, gender, weight, height, body surface area, classification of the American Society of Anesthesiologists, preoperative left ventricular ejection fraction, haemoglobin or creatinine levels at any of the different times, or coagulation variables. Surgery related data (aortic cross-clamping, CPB time, CPB minimum temperature) were also similar. No significant

between group differences were found for duration of mechanical ventilation or length of endotracheal intubation (p> 0.05) (Table-1).

Mean blood loss through the mediastinal and pleural drains was 585±114.6 mL (mean±SD) in group-A and 584±92.39 mL in the group B the difference was not statistically significant (Table-2).

The transfusion rate was 49.6% in group-A and 50.4% in group-B (p=0.33). The number of units of packed red cells transfused per patient was 0.32±1.2 in group-A and 0.52±1.2 in group-B. Thus, the difference was not significant (p=0.530). We did not find any difference in final haemoglobin levels at ICU discharge. Four patients in group-A and six patients in group B received FFPS platelets (Table-2). Excessive bleeding, defined as more than 750 mL in 24 hours, was observed in 9 patients (6.6%), five in group-A and four, in group-B. The difference was not statistically significant (p=0.456). However, only three (2.2%) of these patients were re-operated for excessive bleeding (Table-3) which showed surgical bleed.

Time spent intubated in the ICU was significantly greater for patients with excessive bleeding but this did not prolong their ICU or hospital stay.

There was no significant difference in pre and postoperative creatinine values in both the groups (Table-1).

No allergic reactions related to study drug were observed in either group.

Table-1: Demographic, haemostatic and surgical characteristics of the patients

	Group A (n= 68)	Group B (n=69)	*p*-value
Patient related variables			
Age in years	55.15±7.90	55.41±9.52	0.863
Weight (kg)	69.28±11.17	72.86±12.66	0.082
Height (cm)	167.74±10.38	166.06±11.13	0.364
Body surface area (m^2)	1.77±0.17	1.76±0.18	0.747
Ejection Fraction (%)	50.91±8.47	50.33±7.76	0.677
Preoperative haemoglobin (g/L)	14.39±1.40	13.94±1.38	0.057
Post operative haemoglobin (g/L)	10.69±0.99	10.39±1.09	0.095
Preoperative creatinine (mg/dl)	0.96±0.17	0.93±0.19	0.287
Post operative creatinine (mg/dl)	0.98±0.21	0.96±0.24	0.601
Surgery-related variables			
Minimal CPB-temperature (°C)	28.99±1.25	28.84±1.09	0.472
CPB time (min)	83.59±15.18	84.78±14.08	0.634
Cross-clamp time (min)	49.87±9.50	48.83±7.81	0.484
Minimal haematocrit on CPB (%)	23.54±2.78	23.11±2.70	0.362
Intubation time (hours)	6.00±2.14	5.88±2.02	0.73
ICU stay (days)	2.07±0.26	2.13±0.54	0.435

Table-2: Post-operative total blood loss and transfusion

	Group A (n=68)	Group B (n=69)	*p*-value
Total blood loss (mean±SD) mL	585.15±114.64 mL	584.35±92.39 mL	0.964
Transfused patients (%)	22(32.3%)	36(52.7%)	0.686
PRBC (units/group)	18	30	0.400
FFP and platelets	4	6	0.341
PRBC (units/patient) Mean ± SD (95% CI)	0.32 (0.6–1.1)	0.52 (0.5–1.2)	0.530

PRBC, packed red blood cells; FFPS, fresh frozen plasma; CI, confidence interval.

Table-3: Outcome events by study group

	Group A (n=68)	Group B (n=69)	*p*-value
Allergic reaction	Nil	Nil	Nil
Excessive bleeding	5	4	0.456
Reopening	2(1.5%)	1(0.7%)	0.554

DISCUSSION

Excessive bleeding and increased transfusion requirement may lead to adverse outcome in cardiac surgery.[17,18] A high transfusion rate was demonstrated even in low-risk cardiac patients.[19] Tranexamic acid have been used successfully to reduce bleeding and allogeneic blood transfusion after cardiac surgery[20] but infusion and bolus form of tranexamic acid were not compared in CABG patients.

This trial has demonstrated that both modalities of administering tranexamic acid significantly reduce total blood loss after first-time CABG surgery as results are comparable to other studies in which tranexamic acid was used alone or compared with aprotinin.[14,21] Both treatment group doses were similar 30 mg/kg and equally effective in this regard. The apparent trend towards a lower rate of transfusion in the two groups did not reach statistical significance however. Likewise, final haemoglobin was very similar for all patients upon ICU discharge and intubation time and ICU stay was also comparable between the groups.

Those studies which used more liberal transfusion criteria that is hematocrit less than 30% rather than 25% and in which patients bleed more than ours can more easily demonstrate an effect of tranexamic acid on transfusion requirement. This is the reason why, among our patients, transfusion rates did not reach statistical significance, as this study was underpowered to evaluate such an effect. However, according to two meta-analysis on the various pharmacological strategies used to decrease excessive blood loss in cardiac surgery, tranexamic acid decreases postoperative transfusion. In the first one, Laupacis and Fergusson[2] observed that different

dosing regimens of tranexamic acid were administered in the trials reviewed, different blood transfusion triggers were used, and small samples were enrolled in most of the studies analyzed. In the second meta-analysis, Levi *et al*[3] reported that there was evidence that tranexamic acid decreases perioperative blood loss, need for transfusion, need for reopening and mortality when only trials with complicated cardiac surgery were analyzed. No trial has established which dose is the most efficacious, and dosage regimens studied include such differences as 10 mg/kg followed by an infusion of 1 mg/kg or only an intravenous bolus of 20 mg/kg, 50 mg/kg or 100 mg/kg tranexamic acid, respectively.[22–25]

We used modality of a single bolus dose of 30 mg/kg tranexamic acid as described by Pleym *et al*[14] to be compared with commonly used standard modality with continuous infusion regimen, as described by Casati V *et al*[8], demonstrated in a prospective, randomized, double-blinded, placebo controlled trial that the single bolus dose of 30 mg/kg tranexamic acid before start of CPB reduced bleeding after primary CABG in patients treated with aspirin until the day before surgery. In that study, CPB times were about 62±22 minutes that the single bolus dose guaranteed adequate concentrations of the drug for the entire period of surgery. In our study CPB time was slightly longer that is 83.59±15.18 minutes. This time is also comparable with CPB time in the study of Pleym *et al*. The total blood loss in our study was 585.15±114.64 mL in group A and 584.35±92.39 mL in group B. Thus, it was reasonable for us to assume that a single bolus of 30 mg/kg tranexamic acid might also be effective to reduce blood loss in cardiac surgery procedures with an approximately 45-minute surgical time before and after CPB respectively and CPB times around 100 minutes.

Incidence of reoperation for haemorrhage in cardiac surgery vary between 3% and 14%[26] and this event consumes hospital resources by increasing the operative time and blood product usage, as well as the need for mechanical ventilation, intensive care and longer hospitalization.[16,27] Excessive postoperative bleeding can lead to adverse outcome secondary to re-exploration, transfusion and end-organ injury;[4,5,24] however, a variety of definitions of excessive postoperative bleeding have been proposed in cardiac surgery. In our study, we defined it post op as greater than 750 mL/h over a 24-hour period. With this definition, we found that approximately 6.6% of patients in both treatment groups (nine patients) lost more than that amount, but only 2.1% of the patients needed reoperation because of micro vascular bleeding two in group A and one in group B. Moulton *et al*[5] demonstrated that less than half of re-operated patients had a surgical cause for bleeding, but our finding were opposite as surgical cause was found in all the re-operated cases. It is evident that those patients with excessive bleed who were not re-operated benefited from prophylactic use of tranexamic acid in any modality.

There are few limitations of this study like it was not primarily designed to consider other variables regarding comorbid conditions such as diabetes, hypertension and long-term morbidity and mortality after hospital discharge, and it was underpowered to evaluate either the effect on transfusion or on the prevalence of perioperative thrombotic complications. Clearly, such an analysis would require the enrolment of hundreds of patients per group to avoid statistical error. Another limitation was the lack of laboratory analysis to evaluate the differences in fibrinolysis activation between the two study groups, particularly during the period before heparin administration. Such analysis is not available in our hospital. A last limitation of our study is that it did not include a formal cost-benefit analysis of the use of tranexamic acid and transfusion requirements after CABG, reason of excluding such an analysis was that tranexamic acid is an inexpensive antifibrinolytic agent and all the studied patients were at a low baseline risk of bleeding and blood bank products would not be extensively needed.

CONCLUSION

This study has shown that tranexamic acid in a single bolus of 30 mg/kg is as effective as continuous infusion of same dose for decreasing postoperative bleeding after primary, elective CABG procedures. However, there were no significant differences in clinically relevant endpoints. We would recommend a single-dose of tranexamic acid after heparin administration for safe routine use in patients and clinical settings with a low baseline risk of bleeding, and specifically in patients undergoing conventional uncomplicated primary CABG surgery. However, a prospective, randomized, controlled trial enrolling a homogenous population is needed to define the efficacy of a single-dose of tranexamic acid in patients with a high risk of bleeding. Such a study should systematically consider postoperative thromboembolic complications and clinically relevant outcomes, as well as undertake a cost-benefit analysis of the use of tranexamic acid in comparison with other commonly used antifibrinolytic agents.

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