The Efficacy of Tranexamic Acid in Cardiac Surgery Requiring Cardio-Pulmonary Bypass (CPB) to Reduce Post-Operative Blood Loss and Requirement of Allogenic Blood Transfusion

Abhijeet Shitole[1], Sharanagouda Patil[2], Shilpi Sharma[2], Anand Vagarali[3], Samrat Madnaik[4], Jabbar Momin[5]

ABSTRACT

Introduction: Cardiac surgery, owing to its invasiveness, need of anticoagulation, exposure to extracorporeal circulation (CPB) and relatively longer duration, is known to be associated with an increased risk of perioperative blood loss and allogeneic blood transfusions. Excessive bleeding requiring allogenic blood and blood components transfusion after cardiopulmonary bypass (CPB) is a common complication of cardiac surgery imparting detrimental health and economic consequences. Many techniques like preoperative autologous blood collection (PAC), Acute normovolumic hemodilution (ANH), use of miniaturized CPB circuit and use of ultrafiltration during conduct of cardiopulmonary bypass (CPB) have been applied in the past to conserve the blood during perioperative period in cardiac surgery. Current study aimed to observe the efficacy of Tranexamic acid used during intraoperative period on post-operative blood loss and requirement of allogenic blood and blood products transfusion in cardiac surgical patients requiring cardiopulmonary bypass (CPB).

Material and methods: 120 adult patients undergoing cardiac surgery requiring elective cardiopulmonary bypass (CPB) were categorized into 2 groups. Study ("TXA") group was subjected to administration of tranexamic acid (20 mg/kg in divided doses). The 1st dose (10 mg/kg) was given before initiation of CPB, 2nd dose (5 mg/kg) was given during rewarming on CPB and 3rd dose (5 mg/kg) was given after weaning off CPB along with protamine. The control ("NS") group patients received normal saline as a placebo. Statistical analysis was done using "z test".

Results: "TXA" group had significantly lower post-operative bleeding and lesser requirement of allogenic blood and blood products transfusion. The mean post-operative blood loss in "TXA" group was 427.42+/- 225.18 ml vs. 728.67+/-301.33ml in "NS" group. The mean PCV units transfused post operatively in 72 hours in "TXA" group was 0.20+/-0.44 units vs. 0.67+/-0.60 in "NS" group. Patients in "TXA" group did not require any FFP or platelets unit in contrast to "NS" group where few patients required these products.

Conclusion: The use of Tranexamic acid during intra-operative period in patient undergoing cardiac surgery requiring cardiopulmonary bypass circuit significantly reduces the post-operative bleeding and requirement of allogenic blood and blood products transfusion.

Keywords: Antifibrinolytics, Tranexamic Acid, Allogenic Blood Transfusion, Cardio Pulmonary Bypass (CPB).

INTRODUCTION

Cardiac surgery, owing to its invasiveness, need of anticoagulation, relatively longer duration and exposure to extracorporeal circulation (CPB), is known to be associated with an increased risk of perioperative blood loss and allogeneic blood transfusions.[1] Excessive bleeding requiring transfusion of allogenic blood components after cardiopulmonary bypass (CPB) is a common complication of cardiac surgery imparting detrimental health and economic consequences.[2,3]

Transfusion packed red blood cells (PRBCs) irrespective of the number of units used, has been associated with a dramatically increased rates of morbidity, mortality and health care expenditure in patients undergoing coronary artery bypass grafting (CABG).[4] Requirement of allogenic blood product transfusion and reoperation for bleeding, both, have been associated with adverse clinical outcomes.[1,5]

Many techniques have been applied in the past to conserve the blood during perioperative period in cardiac surgery like preoperative autologous blood collection (PAD), Acute normovolumic hemodilution (ANH), Miniaturization of circuit (miniaturized circuits) and use of ultrafiltration during conduct of cardiopulmonary bypass (CPB).[6] Implementation of a multidisciplinary Blood management team involving

[1]Assistant Professor, Department of Cardiac Anaesthesia, JN Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka, [2]Professor, Department of Cardiac Anaesthesia, JN Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka, [3]Ex Post Graduate Clinical Perfusionist, JN Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka, [4]Professor, Department of Cardiac Anaesthesia, JN Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka, [5]Assistant professor, Department of Cardiac Anaesthesia, JN Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka, [6]Consultant KLES Dr. Prabhakar Kore Hospital, Nehru Nagar Belagavi, Karnataka, India

Corresponding author: Sharanagouda Patil M.D, Professor, Dept of Cardiac Anaesthesia, 1st Floor Krishna Wards, KLES Dr. Prabhakar Kore Hospital, Nehru Nagar, Belagavi, Karnataka, India -590010.

How to cite this article: Abhijeet Shitole, Sharanagouda Patil, Shilpi Sharma, Anand Vagarali, Samrat Madnaik, Jabbar Momin. The efficacy of tranexamic acid in cardiac surgery requiring cardio-pulmonary bypass (CPB) to reduce post-operative blood loss and requirement of allogenic blood transfusion. International Journal of Contemporary Medical Research 2019;6(8):H15-H21.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.8.39

a surgeon, anesthesiologist, perfusionist and hematologist aiming at meticulous surgical and perioperative hemostasis, restrictive transfusion policy may therefore, contribute to a reduction in transfusion requirements, health care costs and an improved surgical outcome. The impact of cardiopulmonary bypass (CPB) distinguishes cardiac surgery from other surgical specialties.[6,7] Hyper-fibrinolysis is one of the important contributors to increased bleeding. This knowledge has led to the use of anti-fibrinolytic agents especially in procedures performed under cardiopulmonary bypass.[7] Antifibrinolytics are frequently used in patients placed on CPB. The two available lysine analogs, ε-aminocaproic acid and tranexamic acid, bind to lysine binding sites on plasminogen and fibrinogen and thereby inhibit plasminogen activator and plasmin release.[7] When administered before CPB, these agents clearly inhibit fibrinolysis, decrease mediastinal bleeding.[7] Use of antifibrinolytic agent aprotinin has shown to reduce intraoperative and post-operative bleeding in cardiac surgical patients.[8] In the present study, effect of tranexamic acid used during intraoperative period on post-operative blood loss and requirement of allogenic blood transfusion is evaluated. In updated European guidelines on perioperative blood conservation strategies in cardiac surgery, the administration of antifibrinolytics in perioperative period is recommended as class I indication with level of evidence B.[8] Guidelines also state that further prospective studies are needed to support this evidence.[8] With this background, the study was planned to strengthen the this evidence for the practice of evidence based medicine (EBM). We hypothesized that the use of antifibrinolytics during perioperative period where the fibrinolytic activity is at its peak will help reduce the postoperative blood loss and requirement of allogenic blood transfusion thus reducing the ICU stay, improved patient outcome and reduction in health care cost.

Current study aimed to observe the efficacy of Tranexamic acid used during intraoperative period on post-operative blood loss and requirement of allogenic blood and blood products transfusion in cardiac surgical patients requiring cardiopulmonary bypass (CPB).

MATERIAL AND METHODS

This randomized prospective case-control study was conducted in adult cardiothoracic surgical unit of a quaternary care hospital in Northern Karnataka, India. After obtaining institutional ethical committee clearance and informed written consent, 120 adult patients undergoing elective open heart surgery requiring cardiopulmonary bypass (CPB) were randomly categorized into 2 groups. "TXA" group (study) received Tranexamic acid 20 mg/kg in three divided doses during intra-operative period. 1st dose of tranexamic acid (10 mg/kg) was given before heparin administration and initiation of cardiopulmonary bypass (CPB). 2nd dose of tranexamic acid (5 mg/kg) was given during rewarming on CPB. The 3rd dose of tranexamic acid (5 mg/kg) was given along with protamine during heparin reversal after weaning off from cardiopulmonary bypass (CPB). "NS" group (control) received normal saline as a placebo.

Patient's Inclusion Criteria were Age between 18 years and 80 years, weight > 40 kilograms and baseline hematocrit (HCT) > 30%. Patients with evidence and history of smoking, Chronic kidney disease (CKD), Adult cyanotic congenital heart diseases (ACHD), Bleeding diathesis, Hemophilia and other Bleeding tendencies were excluded from the study. Emergency surgeries in which antiplatelet and thrombolytic therapy has not been stopped well before surgery (not less than 5 days prior to surgery), patients with INR > 1.50 and Platelet count < 1.5 lacks/cumm were also excluded from study. The Demographic parameters like Age, Sex, Body surface area were recorded. Baseline hemoglobin (Hb) gram%, hematocrit level (HCT), Central Venous Pressure (CVP) (as an indicator of intravascular volume status), Activated Clotting Time (ACT) were noted.

The trends in perioperative hematocrit (HCT), peri-operative blood loss, requirement of allogenic blood and blood products transfusion till 72 hours after surgery were noted. The transfusion trigger for allogenic blood use was kept as hematocrit (HCT) of < 21% during conduct of CPB and <25% in post-operative period.

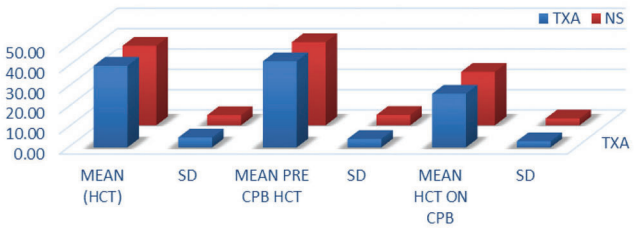
STATISTICAL ANALYSIS

Data was obtained and analyzed by using Microsoft excel version 2010. Descriptive analysis was done to summarize qualitative data by using mean and standard deviation (Mean+/-SD) {SE}. The intergroup comparison of explanatory variables was done and analyzed with "Z -test". P value of <0.05 was considered as significant. P <0.001 was considered as highly significant. P >0.05 was considered non-significant.

RESULTS

120 adult patients undergoing open heart surgery on elective cardiopulmonary bypass were categorized to receive either tranexamic acid or normal saline as placebo control (60 in each group).The data obtained was analyzed statistically using the Microsoft excel version 2010. Descriptive analysis was done to summarize qualitative data by using mean and standard deviation. The intergroup comparison of explanatory variables was done and analyzed with "z test". P value of <0.05 was considered as significant. P <0.001 was considered as highly significant. P >0.05 was considered non-significant (table 1 and graph 1)).

There was statistically significant difference in the mean age



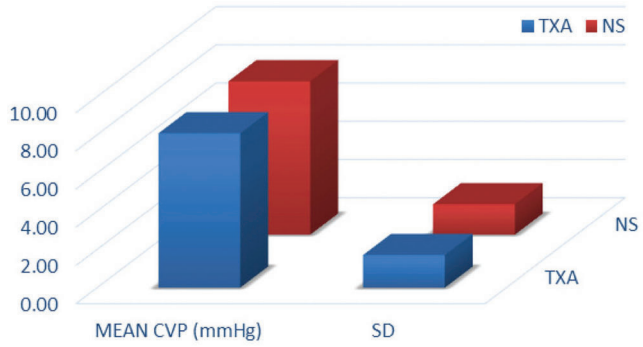
Graph-1: Comparison of Baseline Hematocrit (HCT)%, Pre -CPB Hematocrit% and Hematocrit% on CPB in TXA (study) Vs. NS (control) Group

Study Variable	TXA (Study) Group (Mean +/- SD) {SE} (n=60)	NS (Control) Group (Mean +/- SD) {SE} (n=60)	Z Score	P value
Age (years)	54.33 +/-11.85 {1.53}	47.07 +/- 13.81 {1.78}	3.09	< 0.05
Sex	Male;36 (60%), Female; 24 (40%)	Male; 48 (80%), Female;12 (20%)		
Body Surface Area (BSA) (M^2)	1.68 +/- 0.21 {0.03}	1.53 +/- 0.22 {0.03}	3.77	< 0.05
Baseline Haematocrit (HCT) (%)	39.16 +/- 5.03 {0.65}	40.18 +/- 4.87 {0.63}	-1.13	>0.05
Baseline CVP (mmHg)	8.03 +/- 1.59 {0.21}	8.08 +/- 1.71 {0.22}	-0.17	>0.05
Baseline Activated Clotting Time (ACT) (sec)	109.53 +/- 7.74 {0.99}	111.33 +/- 7.27 {0.94}	-1.31	>0.05
Pre CPB Haematocrit (HCT) (%)	40.93 +/- 5.14 {0.66}	42.39 +/- 4.18 {0.54}	-1.71	>0.01
Haematocrit on CPB (%)	26.32 +/- 3.41 {0.44}	26.44 +/- 3.05 {0.39}	-0.20	>0.05
CPB Duration (Minutes)	91.90 +/-9.51{1.23}	93.37 +/- 10.99{1.42}	42.12	>0.05

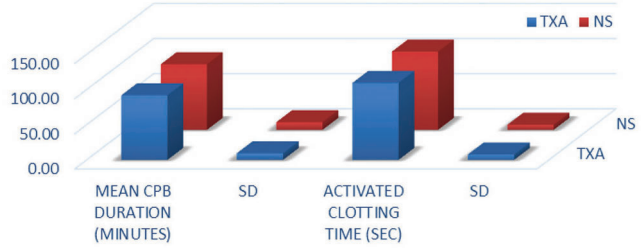
Table-1: Comparison of Demographic Variables and Baseline Study Variables between TXA (Study) group and NS (Control) group.

Outcome variable	TXA (Study) Group (Mean +/- SD) {SE} (n=60)	NS (Control) Group (Mean +/- SD) {SE} (n=60)	Z Score	P value
Total Drainage (Blood Loss) in 72 hours (ml)	427.42 +/-225.18 {29.07}	728.67 +/- 301.33 {38.90}	6.20	P< 0.001
Mean total PCV Units used in Perioperative Period	0.67 +/- 0.60 {0.06}	0.20 +/- 0.44 {0.08}	4.84	P<0.001
Mean total Thrombocyte Units used in Perioperative Period	0.00 +/-0.00 {0.00}	0.32 +/- 0.95 {0.12}	2.59	P <0.001
Mean total FFP Units used in Perioperative Period	0.00 +/- 0.00 {0.00}	0.20 +/- 0.78 {0.10}	1.99	P <0.001
Cost of Blood Transfusion (INR)	172.50 +/- 350.80 {45.29}	1025.17 +/- 1525.14{196.90}	4.22	P <0.001
Total Stay in Intensive Thoracic Unit (Days)	4.05 +/- 1.28 {0.17}	5.23 +/- 2.59 {0.33}	3.17	<0.05

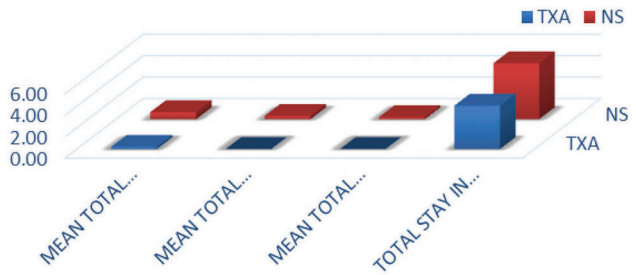
Table-2: Comparison of outcome variables in TXA (Study) Group and NS (Control) group



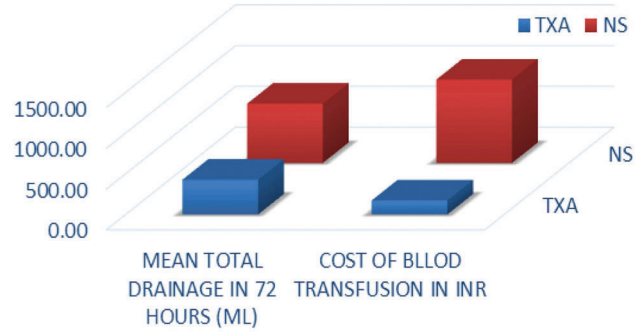
Graph-2: comparison of pre CPB central venous pressure (CVP) as an indicator of Intravascular volume status.



Group-3: Comparison of Pre CPB Activated Clotting Time(ACT) (seconds) and Mean CPB Duration (minutes) in TXA (Study) Group Vs. NS (Control) Group



Graph-4: Comparison of Mean PCV, Thrombocytes, FFP Units used in Perioperative Period and Average stay in ITU in Days



Graph-5: Comparison of Total Drainage (Blood Loss) in 72 hours (ml) and Cost of Blood Transfusion (INR)

in years between 2 groups. The mean age in TXA (Study) group was 54.33 +/-11.85 {1.53} Vs 47.07 +/- 13.81 {1.78} in NS (Control) group (P < 0.05). The population in TXA group was relatively younger than the NS group. In TXA (study) group the female patient population was 24 (40%) as compared 12 (20%) in NS (control) group. The male

population in TXA group was 36 (60%) as compared 48 (80%) in NS group. There was statistically significant difference in the mean body surface area (BSA) in 2 groups. The mean BSA in TXA (study) group was 1.55+/- 0.20 {0.03} m^2 compared to 1.67+/-0.21 {0.03} m^2 in NS (control) group (P<0.05). There was statistically significant difference between the two groups(table 2 and graph 2,3).

There was no statistically significant difference in baseline hematocrits of both the groups hence the baseline hematocrits were comparable. The mean Baseline hematocrit was 39.16 +/- 5.03 {0.65} % in TXA group Vs. 40.18 +/- 4.87 {0.63}% in NS group (P>0.05). There was no statistically significant difference in pre CPB volume status (preload) between two groups. The mean Central Venous Pressure (CVP) was 8.03 +/- 1.59 {0.21} mmHg in TXA (study) group compared to 8.08 +/- 1.71 {0.22} in NS (control) group (P>0.05). Hence, the groups were comparable with respect to pre CPB volume status. the Baseline Hematocrit (HCT) was 40.93 +/- 5.14 {0.66} % compared to 42.39 +/- 4.18 {0.54}% in NS group (P>0.01). Hence, there was no statistically significant difference between the baseline hematocrits between two groups. Baseline HCT was comparable. The Baseline Activated Clotting Time (ACT) in TXA (study) group was 109.53 +/- 7.74 {0.99} seconds Vs 111.33 +/- 7.27 {0.94} seconds in NS (control) group (P >0.05). There was no statistically significant difference in two groups thus, Baseline ACT was comparable in both the groups. The comparison on CPB Hematocrit (HCT) showed no statistically significant difference in both the groups. There were 3 serial hematocrits done during cooling, at the start of rewarming and just before weaning from CPB as an institutional protocol. The mean HCT of these hematocrit was taken for statistical analysis. The Mean HCT on CPB was 26.32 +/- 3.41 {0.44}% in TXA (study) group Vs. 26.44 +/- 3.05 {0.39}% in NS (control) group (P>0.05).

The drop in HCT level below 25% was kept as a transfusion trigger for transfusion PCV unit to the patient in postoperative period. The mean total PCV unit transfused in 72 hours in TXA (study) group were 0.20+/-0.44 {0.17} units as compared to 0.67+/-0.60 {0.33} units in NS (control) group. There was statistically highly significant difference (P<0.001) noted between the two groups in relation to total PCV units Usage. The study group required significantly lesser PCV unit transfusions to maintain HCT above 25%. 35 patients in control group required transfusion of 1 PCV unit while 10 patients of study group required transfusion of 1 PCV unit. The Fresh Frozen Plasma transfusion was considered in peri-operative period by the surgeons when there was evidence of "wet" surgical field or based on nature of chest tube drainage in first 24 hours. TXA (Study) group did not receive any FFP for bleeding in Peri-operative period. The control group did require it. Total 12 FFP units were used in NS (Control) group as compared to None in TXA (Study) group. This shows there was highly significant statistical difference between two groups in relation to need of FFP transfusion(graph 4).

The Thrombocytes transfusion was considered in peri-operative period by the surgeons when there was evidence of "wet" surgical field even after heparin reversal or continued chest drainage without much evidence of surgical bleeding. TXA (Study) group did not receive any thrombocytes transfusion for bleeding in peri-operative period. The NS (control) group did require the thrombocytes transfusion in peri-operative period. NS (Control) group required 19 thrombocytes units compared to none in TXA (Study) group. This shows there was highly significant statistical difference between two groups in need of thrombocytes transfusion. The cost of blood and blood product transfusion was calculated as a total perioperative units of blood and blood product transfused. The intergroup comparison of total cost of blood transfusion at the end of 72 hours after surgery was analyzed. The mean cost of blood transfusion in TXA (study) group was 172.50+/- 350.80 {45.29}Rs compared to 1025.17+/- 1525.14 {172.90} Rs in NS (control) group. This shows that there is a statistically highly significant difference in relation to cost of blood transfusion between two groups. Cost of transfusion being significantly low in TXA group. The intergroup comparison of total ITU stay was done as a secondary objective of this study. The mean ITU stay in TXA (study) group was 4.05+/-1.28 {0.17} days as compared to 5.23+/-2.59{0.33} days in NS (control) group. This suggests that there was highly significant difference between two groups in relation to ITU stay. The mean ITU stay in TXA (study) group was significantly lower (graph 5).

DISCUSSION

The baseline HCT of "TXA" (Study) group and "NS" (control) group was comparable. The baseline HCT of study group was 40.18+/- 4.18% vs. 39.16+/- 5.03% in control group. The mean HCT on cardio pulmonary bypass (CPB) in study group was 26.44+/- 3.05% vs. 26.32+/- 3.41% in control group. These HCT values were also comparable. The mean priming volume used was also comparable (1353.06+/- 145.43 ml in study group vs. 1370.55+/- 162.63 ml in control group). There was significantly lower postoperative drainage (bleeding) in study group as compared to control group (total drainage at the end of the 72 hours was 427.42+/- 225.18 ml in study group as compared to 728.67+/- 301.33 ml in control group). This can be contributed to antifibrinolytics used in study group which prevent excessive clot lysis in immediate post-operative period. The use of tranexamic acid 20 mg/kg in 3 divided doses, half pre bypass, $1/4^{th}$ on CPB and $1/4^{th}$ with protamine during heparin reversal appeared to be effective regimen for reducing the post-operative blood loss in cardiac surgical patient performed on CPB.

The use of blood and blood products in postoperative period was significantly higher in "NS" group as compared to "TXA" group. The mean PCV used was 0.20+/-0.44 units in "TXA" study group as compared to 0.67+/-0.60 units in control group. The "TXA" study group required significantly lesser PCV unit transfusions to maintain HCT above 25%. 35 patients in "NS" control group required transfusion of 1 PCV unit while 10 patients of "TXA" study group required transfusion of 1 PCV unit. One patient in "NS" control

group required transfusion of 3 PCV units and another one patient required 2 PCV units transfusion to maintain HCT >25%. Only 1 patient in the "TXA" study group required transfusion of 2 PCV units. "TXA" Study group did not receive any FFP for bleeding in post-operative period. The "NS" control group did require the FFP transfusion in post-operative period. One patient in "NS" control group required 5 FFP units, 3 patients required 2 FFP units and one patient required one FFP transfusion. "TXA" Study group did not receive any platelet for bleeding in post-operative period. The "NS" control group did require the platelet transfusion in post-operative period. Three patients in "NS" control group required 4 platelet units, two patients required 2 platelet units and 3 patients required 1 platelet unit transfusion. These observations suggest that application of multi model blood conservation technique significantly reduce allogenic blood and blood products requirements transfusion in post-operative period in cardiac surgically patient. It also suggests that the mean HCT is maintained relatively more stable and within satisfactory levels (30-35%) when these techniques were applied.

In spite of more usage of PCV units, FFP units and platelet units in "NS" control group as compared to "TXA" study group, there was significantly higher bleeding in "NS" control group. This can highlight that, the allogenic blood and blood product usage do not reduce bleeding in cardiac surgical patients if the use of antifibrinolytics and other blood conservation techniques like autologous blood collection and re transfusion, ultra-filtration are not used routinely.

As the allogenic blood and blood product usage was significantly lesser in "TXA" study group as compared to "NS" control group, the cost of transfusion were significantly lower. This suggests that the application of multi model blood conservation techniques significantly reduces the cost of allogenic blood transfusion by reducing the usage of allogenic blood and blood product transfusion.

Myles PS, Smith JA et al. in RCT called The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) compared TXA with placebo in patients having CABG surgery and demonstrated a reduction in the risk for reoperation due to major hemorrhage (RR 0.36, 95% CI 0.21–0.62; P<0.001) and in the need for the transfusion of any blood products (37.9% vs 54.7%; P<0.001).[11] In a systematic review and cumulative meta-analysis by, it was shown that TXA reduced the pooled risk ratio for blood transfusion in patients having cardiac surgery compared with the controls (RR 0.65, 95% CI 0.60–0.70; P<0.001).[13] The most significant reported side effect of TXA was convulsive seizure.[13] Doses in the range of 50mg/kg to 100mg/kg were not safer in terms of seizures (0.7 vs 0.6%, respectively), but the higher dose significantly reduced blood loss (P=0.026) and PRBC transfusion. In present study, the total dose of tranexamic acid used was 20 mg/kg. According to the available literature, this dose has not been associated with seizures. The dose increment from 20 mg/kg to 50 mg/kg do not have any added clinical advantage rather it increases the probability of seizures in patient. In present study none of the subjects experience seizures.

Sharma V Et al used the recommended dose from the German package insert of TA (Tranexamic Acid) is a bolus of 1000 mg for the patient and 500 mg for the CPB circuit followed by a continuous infusion of 400 mg h^{-1} during surgery.[14] The dosing regimen used in present study was lower than German recommendation. The bolus pre CPB dose was restricted to 10 mg/kg and during CPB to 5 mg/kg. The Post CPB dose was given as a bolus dose of 5 mg/kg instead of continuous infusion. The restricted dosing was preferred as there is no added advantage of dosing more than 20 mg/kg if fibrinolysis is a concern. Instead, with higher regimens result in precipitation of adverse effects like seizures. Koster A Et al studied the incidence of seizures as adverse effect of TA, Out of enrolled 11529 subjects, 73 CS occurred. The incidence of CS was 2.5% in the TA group and was approximately twice as high compared with the reference group TA and the reference groups, the duration of mechanical ventilatory support, ICU stay, and in-hospital mortality was significantly higher in patients experiencing CS compared with CS-free patients. Even moderate TA doses of on average 24 mg kg^{-1} are associated with an increased risk to experience CS, which after PS adjustment was attenuated, but still 70% higher compared with the reference group. In addition, TA use was an independent predictor of in-hospital mortality, especially in patients with open-heart surgery procedures. Tranexamic acid was an independent predictor of postoperative convulsive seizures in cardiac surgical patients, moreover, the risk of seizures was significantly higher in patients receiving tranexamic acid as an infusion. The cumulative doses of > 80 mg/kg/l was responsible for seizures. Evidence of acute organic brain injury was seen in only 16% of patients with postoperative convulsive seizures.[15] In present study, there was no evidence of convulsion in any patient. In one AVR subject, There was TIA like episode documented, but had a normal CT finding and recovered spontaneously.

Srikrishna M R, Sachin T et.al. Studied the Multi-modality blood conservation strategy in open-heart surgery. 310 consecutive adult patients undergoing open-heart surgery over a period of 8 months were retrospectively reviewed to assess the comprehensive blood conservation protocol. Preoperative demographic characteristics, intraoperative data and postoperative variables were taken. Only 54 patients (17.42%) received one or more units of allogenic transfusions either intraoperatively or postoperatively until discharge. A total number of 184 units, 135 units of packed red blood cell (RBC), 24 units of fresh frozen plasma and 25 units platelet concentrate were used for transfusion. Of the 135 units of packed RBC used, only 34 units were transfused in the postoperative period. They maintained Mean hemoglobin at the time of discharge was 9.8 Grams% (8.9–12.6 Grams%). As they concluded that, a standardized multidisciplinary approach to blood conservation in cardiac surgery decreases bleeding and transfusion requirements in a safe and cost effective manner.[16] In present study, strict transfusion protocols were followed including perioperative

antifibrinolytic therapy.

Gregory A. Nuttall, William C. Oliver et al compared the Blood-conservation Strategies in Cardiac Surgery Patients at High Risk for Bleeding. They enrolled 168 patients were randomly assigned to 4 groups to receive Aprotinin as a loading dose of 200 ml (280 mg) over 20–30 min) or continuous infusion of 50 ml/h (70 mg/h) or a "CPB circuit prime" of 200 ml (280 mg). The 4th, placebo group received a normal saline infusion. Intraoperative autologous blood collection (ANH) was done with 12.5% of the patient's calculated whole-blood volume. POC (The laboratory data) was measured preoperatively, 10 min after protamine neutralization of heparin, 90 min after protamine neutralization of heparin, and 24 h after protamine neutralization of heparin were examined using a repeated-measures analysis of variance. They concluded that, though aprotinin is an effective drug for reducing bleeding and prevention of blood transfusions, tranexamic acid and especially tranexamic acid combined with a presumptive platelet-sparing maneuver, such as intraoperative autologous whole-blood collection (ANH), were essentially equally efficacious and much less costly therapies.[17]

Ultrafiltration (UF) and modified ultrafiltration (MUF) help removal of inflammatory mediators which may be a factor responsible for improved hemostasis. In a meta-analysis, done by Boodhwani M Et al, it was shown that ultrafiltration, and particularly modified ultrafiltration, was associated with a reduction in postoperative blood transfusions (−0.73 units; 95% CI −1.16 to −0.31).[18] In Present study, patients of both the groups were subjected to Ultrafiltration to avoid excess hemodilution as an institutional protocol for conduct of CPB. Luiciani GB Et al, In a large RCT showed lower transfusion requirements in patients subjected to ultrafiltration compared to whom ultrafiltration was not implemented.[19] in present study lower rate of transfusion in study group may indicate added advantage of antifibrinolytics use over UF.

In one of the matched pair analysis with 432 patients, done by Martin K Et al, the preoperative autologous blood donation was associated with a reduction in the transfusion rate of PRBC from 55% to 32% and a 50% reduction in the administration of FFP and platelet concentrate (PLTC).[20] A nested case-control study by Lewis CE Et al, further revealed that preoperative autologous blood donation reduced PRBC transfusions by 18.3% in valve surgery. Lack of preoperative Hb and hematocrit data however, limited the study.[21] In present study, stringent attention was given to preoperative data. The baseline parameters were compared with the post-operative data for assessment of perioperative trends.

A recent meta-analysis done by Patel Et.al compared restrictive (Hb 70–80 g/l) and liberal (Hb 90–100 g/l) transfusion strategies using data from 6 RCTs with 3352 patients, showing a 30% reduction in the number of deaths in the restrictive regimen group (OR 0.70, 95% CI 0.49–1.02; P=0.060). in present study, the restrictive regimen was used for transfusion requirement.[22]

Barile L, Fominskiy E Et al, systematically reviewed and meta-analyzed 29 RCTs to investigate the effect of ANH using various solutions like colloid, albumin and crystalloid volume replacement on allogeneic PRBC transfusion requirements in adult and pediatric cardiac surgical procedures.[18] The majority of the studies included had no predefined transfusion protocols. In the 21 studies with allogeneic blood transfusion was a predefined end point. ANH groups received fewer PRBCs (−0.79 units; 95% CI −1.25 to −0.34; P=0.001). ANH was associated with a significant, but clinically irrelevant, reduction in postoperative bleeding (−0.64 ml; 95% CI −0.97 to −0.31; P<0.0001).[18] In present study, the transfusion protocol was predefined. ANH was not kept as a mandatory protocol to study group.[23]

CONCLUSION

The use of antifibrinolytic agent Tranexamic acid during intraoperative period in 3 divided doses as 10 mg/kg before initiation of cardiopulmonary bypass (CPB), 5 mg/kg during conduct of CPB and 5 mg/kg after heparin reversal constituted a safe and effective method of reducing the post-operative bleeding and requirement of allogenic blood and blood product transfusion to maintain desirable hematocrit (HCT) in post-operative period in patients undergoing cardiac surgery performed on cardiopulmonary bypass. Reduction in the rate of allogenic blood were responsible for lesser stay in ITU, cost effectiveness and improved surgical outcome and reduction in morbidity. The lesser ITU stay was responsible for early recovery and transfer to post-operative wards.

Authors recommend routine use of antifibrinolytic agent Tranexamic acid during intraoperative period to reduce post-operative bleeding and allogenic blood transfusion in cardiac surgical patients.

Limitations

It was a randomized prospective study. The distribution of the population according to age and the sex was not comparable. The population which got enrolled to study group was relatively younger compared to control group.

During conduct of study, the other approaches of blood conservation like smaller priming volumes and Intraoperative autologous blood collection were applied. Intraoperative autologous blood collection was done in cases where baseline hematocrit (HCT) was > 40%.

The routine methods of blood conservation like retrograde autologous priming (RAP) and conventional ultrafiltration (CUF) on CPB were used in both the groups as per the institutional protocols of conduct of CPB.

The point of care (POC) testing like Thromboelastography (TEG), Platelet aggregometry were not done to assess the coagulation function in present study, we relied on activated clotting time (ACT) using Actalyke mini ACT machine which uses the celite contact surface technology for activation of clotting and measuring the clotting time.

Key words: Allogenic blood transfusion, Antifibrinolytics, Tranexamic Acid (TXA), Cardio Pulmonary Bypass (CPB), Intensive thoracic unit (ITU).

REFERENCES

1. Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA et al. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 2004;44:1453–62.
2. Antonio Alceu dos Santos, Jose Francisco Baumgratz, Jose Henrique Andrade Vila, Rodrigo Moreira Castro, Rodrigo Freire Bezerra. Clinical and Surgical Strategies for Avoiding or Reducing Allogeneic Blood Transfusions. Cardiol Res. 2016; 7: 84–88.
3. Alan T. Tinmouth, Lauralynn A. McIntyre, Robert A. Fowler. Blood conservation strategies to reduce the need for red blood cell transfusion in critically ill patients. CMAJ. 2008; 178: 49–57.
4. Paone G, Likosky DS, Brewer R, Theurer PF, Bell GF, Cogan CM et al. Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. Ann Thorac Surg 2014;97:87–93; discussion 93–4.
5. Ranucci M, Bozzetti G, Ditta A, Cotza M, Carboni G, Ballotta A. Surgical reexploration after cardiac operations: why a worse outcome? Ann Thorac Surg 2008;86:1557–62.
6. Dhir A. Antifibrinolytics in cardiac surgery. Ann Card Anaesth. 2013; 16:117-25.
7. Dennis T Mangano, Iulia C Tudor, Cynthia Dietzel. Multicenter Study of Perioperative Ischemia Research Group, Ischemia Research and Education Foundation The risk associated with aprotinin in cardiac surgery. N. Engl. J. Med.: 2006, 354;353-65.
8. Ray H. Chen, O.H. Frazier, Denton A. Cooley. Antifibrinolysis and Blood-Saving Techniques. Tex Heart Inst J. 1995; 22:211-5.
9. Valter Casati, Davide Guzzon, Michele Oppizzi, Mariangelo Cossolini et.al. Hemostatic Effects of Aprotinin, Tranexamic Acid and e-Aminocaproic Acid in Primary Cardiac Surgery. Ann Thorac Surg. 1999;68:2252–7.
10. Domenico Pagano, Milan Milojevic, Michael I Meesters, Umberto Benedetto, Daniel Bolliger, Christian von Heymann Et.al. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. European Journal of Cardio-Thoracic Surgery 2018; 53:79–111.
11. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T et al. Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med 2017;376:136–48.
12. Adler Ma SC, Brindle W, Burton G, Gallacher S, Hong FC, Manelius I et al. Tranexamic acid is associated with less blood transfusion in offpump coronary artery bypass graft surgery: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2011;25:26–35.
13. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. Br Med J 2012;344:e3054.
14. Sharma V, Katznelson R, Jerath A, Garrido-Olivares L, Carroll J, Rao V et al. The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11529 patients. Anaesthesia 2014;69:124–30.
15. Koster A, Borgermann J, Zittermann A, Lueth JU, Gillis-Januszewski T, Schirmer U. Moderate dosage of tranexamic acid during cardiac surgery with cardiopulmonary bypass and convulsive seizures: incidence and clinical outcome. Br J Anaesth 2013;110:34–40.
16. Reddy Srikrishna Modugula et.al. Multi-modality blood conservation strategy in open-heart surgery. Interactive CardioVascular and Thoracic Surgery. 2009; 9: 480–483.
17. Gregory A. Nuttall, William C. Oliver, Mark H. Ereth, Paula J. Santrach, Sandra C. Bryant, Thomas A. Orszulak, Hartzell V. Schaff. Comparison of Blood-conservation Strategies in Cardiac Surgery Patients at High Risk for Bleeding, Anesthesiology 2000;92:674-682.
18. Boodhwani M, Williams K, Babaev A, Gill G, Saleem N, Rubens FD. Ultrafiltration reduces blood transfusions following cardiac surgery: a meta-analysis. Eur J Cardiothorac Surg 2006;30:892–7.
19. Luciani GB, Menon T, Vecchi B, Auriemma S, Mazzucco A. Modified ultrafiltration reduces morbidity after adult cardiac operations: a prospective, randomized clinical trial. Circulation 2001;104:I253–9.
20. Martin K, Keller E, Gertler R, Tassani P, Wiesner G. Efficiency and safety of preoperative autologous blood donation in cardiac surgery: a matched-pair analysis in 432 patients. Eur J Cardiothorac Surg 2010; 37:1396–401.
21. Lewis CE, Hiratzka LF, Woods SE, Hendy MP, Engel AM. Autologous blood transfusion in elective cardiac valve operations. J Card Surg 2005; 20:513–8.
22. Patel NN, Avlonitis VS, Jones HE, Reeves BC, Sterne JA, Murphy GJ. Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis. Lancet Haematol 2015;2:e543–53.
23. Barile L, Fominskiy E, Di Tomasso N, Alpizar Castro LE, Landoni G, De Luca M et al. Acute normovolemic hemodilution reduces allogeneic red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis of randomized trials. Anesth Analg 2017;124:743–52.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 08-07-2019; **Accepted:** 02-08-2019; **Published:** 28-08-2019