Comparison of efficacy of two different doses of tranexamic acid in prevention of post operative blood loss in patients with congenital cyanotic heart disease undergoing cardiac surgery

Thushara Madathil, Rakhi Balachandran, Brijesh P Kottayil, K R Sundaram, Suresh G Nair
Departments of Cardiac Anesthesia and Critical Care, and, 1Cardiothoracic and Vascular Surgery, 2Department of Biostatistics, Amrita Institute of Medical Sciences and Research Centre, 3Department of Anesthesiology and Critical Care, Aster Medicity, Kochi, Kerala, India

ABSTRACT
Background: The optimal dose of tranexamic acid in minimizing perioperative bleeding is uncertain. We compared efficacy of two different doses of tranexamic acid in reducing post-operative blood loss and its side effects in patients with congenital cyanotic heart disease undergoing cardiac surgery.

Settings and Design: Prospective observational study at a pediatric cardiac center in South India.

Methods: Consecutive cyanotic patients undergoing cardiac surgery were divided into groups I and II to receive either 10 mg/kg or 25 mg/kg of tranexamic acid administered as triple dose regime after induction, during cardiopulmonary bypass, and after protamine. Post-operative blood loss at 24 hours, blood component utilization, incidence of renal dysfunction and seizures were compared.

Results: Totally, 124 patients were recruited, 62 in each group. The pre-operative variables and cardiopulmonary bypass time were comparable. Patients receiving 25 mg/kg had lower post-operative blood loss compared to patients in lower dose group (8.04 ± 8.89 vs 12.41 ± 19.23 ml/kg/24 hours, P = 0.03). There was no difference in the transfused volume of packed red cells (9.21 ± 7.13 ml/kg vs 12.41 ± 9.23 ml/kg, P = 0.712), fresh frozen plasma (13.91 ± 13.38 ml/kg vs 11.02 ± 8.04 ml/kg, P = 0.19), platelets (9.03 ± 6.76 ml/kg vs 10.90 ± 6.9 ml/kg, P = 0.14) or cryoprecipitate (0.66 ± 0.59 ml/kg vs 0.53 ± 0.54 ml/kg, P = 0.5) in group II and I, respectively. Two patients developed renal dysfunction secondary to low cardiac output in lower dose group. There were no seizures.

Conclusions: Tranexamic acid administered at a dose of 25 mg/kg as triple dose regime is associated with lower post-operative blood loss compared to a lower dose of 10 mg/kg in cyanotic patients undergoing cardiac surgery without causing major adverse effects.

Keywords: Blood loss, cardiac surgery, cyanotic, pediatric, tranexamic acid

INTRODUCTION
Patients with congenital cyanotic heart disease are predisposed to increased perioperative bleeding secondary to coagulation abnormalities including excessive fibrinolysis.[1,2] The risk of bleeding is further aggravated by sequelae of chronic hypoxemia, complexity of surgical repair and sometimes the need for multiple
palliative procedures in cyanotic patients. Tranexamic acid is extensively used in pediatric cardiac surgery as an antifibrinolytic agent to minimize perioperative blood loss and transfusion requirements. Pharmacologically, tranexamic acid is a lysine analog which prevents plasmin formation by blocking the lysine binding sites of plasminogen, thus inhibiting fibrinolysis.[3] Over the last decade, tranexamic acid has evolved into an important tool in the armamentarium of cardiac anesthesiologist for patient blood management in pediatric cardiac surgery. However, there has been no consensus on the optimal dose and administration method of tranexamic acid in pediatric cardiac surgical patients. Chauhan et al. had demonstrated that a triple dose regimen of tranexamic acid, 10 mg/kg after induction, 10 mg/kg in cardiopulmonary bypass (CPB) prime, and 10 mg/kg after protamine was more effective than a single large dose.[8] Studies have also shown that a bolus dose followed by continuous infusion of tranexamic acid can maintain optimal plasma levels and facilitate better pharmacological effects.[8] We sought to compare the efficacy of two different doses of tranexamic acid in decreasing post-operative bleeding after cardiac surgery in patients with cyanotic congenital heart disease. We also sought to compare the utilization of blood and blood products between the two groups. Our secondary objective was to identify the incidence of side effects namely renal failure requiring dialysis and post-operative seizures between the two groups.

METHODS

This was a prospective observational study conducted in a tertiary pediatric cardiac care center in South India. The study period was from 1st September 2013 to 30th September 2014. After obtaining institutional ethics committee approval, a written informed consent was obtained from the parents of all patients. Since there was no similar study in literature comparing the specific doses of tranexamic acid that we employed, this was conducted as a pilot study. All consecutive pediatric patients below the age of 18 years undergoing surgery for cyanotic congenital heart disease were included. Patients with pre-operatively diagnosed bleeding diathesis or seizure disorder were excluded from the study. Two different tranexamic acid dosing regimens were being followed at our institution for the past 1 year based on the perioperative protocols of two different anesthesiology consultants. All patients undergoing surgery in operating room 1 who received a bolus dose of 10 mg/kg tranexamic acid at induction, 10 mg/kg added to cardiopulmonary bypass (CPB) circuit prime and 10 mg/kg after protamine administration constituted group I. Group II constituted patients undergoing surgery in operating room 2 who received a bolus dose of 25 mg/kg tranexamic acid at induction, in CPB prime and after protamine administration.

The standardized institutional protocol for induction of anesthesia in cyanotic pediatric patients was followed in both the groups. The procedure for management of cardiopulmonary bypass was similar in both operating rooms. Two different surgeons of comparable skill and experience performed all the cardiac operations. During surgery, each of the groups received tranexamic acid as a triple dose regime as indicated above. The hematocrit on CPB was maintained between 25 and 30% in both the groups. A thromboelastogram (TEG) was done for all patients after administration of protamine to identify specific coagulation abnormalities after separation from CPB. Post-operative blood component therapy was primarily guided by TEG parameters. PRBC transfusion was typically indicated when hemoglobin concentration was less than 10 g/dL. Blood viscosity can be an important determinant of systemic vascular resistance (SVR) in cyanotic patients and a low hematocrit can sometimes predispose to hypotension in these patients by lowering the SVR. Therefore, we usually target a post-operative hemoglobin concentration of 10 g/dL in cyanotic patients during the first 24 hours after surgery. However, on rare occasions post-operative transfusion practices were modified as per the demands of the surgical team particularly in patients with hemodynamic instability due to hypovolemia in the early post-operative period. All patients were admitted post operatively into a dedicated pediatric cardiac intensive care unit. The patients were monitored for hourly chest tube output, volume of blood and blood components transfused and development of adverse effects related to tranexamic acid namely seizures and renal failure.

The pre-operative, intra operative and post-operative data were collected using a pre-printed proforma. The demographic data and data pertaining to diagnosis and surgical procedure were obtained from patient medical records. Intraoperative variables included CPB time, aortic cross clamp (ACC) time and the degree of cooling during CPB. The primary outcome variables included chest drain output at 24 hours after surgery, need for re-exploration, percentage of patients requiring transfusion of packed red cells, fresh frozen plasma (FFP), platelet concentrate and cryoprecipitate in each of the two groups, and the volume of packed cells and/or blood components transfused. The patients were also monitored for the two potential side effects namely, renal failure requiring dialysis, or post-operative seizures.
Statistical analysis
The data were analyzed using Statistical Package for Social Sciences (SPSS) Version 20.0 (SPSS Inc, Chicago, IL, USA). The data were expressed as frequencies, mean values and standard deviations, or median and range as appropriate. To test the statistical significance of the difference in the mean values between the two groups, Student’s t-test was applied. When there was heterogeneity of variances and non-normal distribution, Mann-Whitney U test was applied. To test the statistical significance of the association between the categorical variables between the two groups, the Chi-square test was applied. P value ≤0.05 was considered to be significant.

RESULTS
Totally, 124 patients were recruited into the study. Sixty-two patients undergoing surgery in operating room 1 and receiving 10 mg/kg bolus dose of tranexamic acid after induction of anesthesia, in CPB prime and after protamine were included into group I. Sixty-two patients undergoing surgery in operating room 2 receiving 25 mg/kg bolus dose of tranexamic acid after induction, in CPB prime and after protamine constituted group II. Preoperative, intraoperative, and post-operative variables were compared between the two groups. The demographic data with respect to gender and age distribution, incidence of re-do surgeries, CPB time, ACC time and frequency of delayed sternal closure were all comparable between the two groups [Table 1]. The post-operative TEG values were also not significantly different between the two groups. Though the R time, an indicator of coagulation factor concentration was numerically higher in group I as compared to group II (6.90 ± 2.3 min vs 5.94 ± 2.86 min), the mean values were falling well within the accepted normal range of R time which indicated normal level of coagulation factors in both the groups of patients. The K time indicating coagulation factor function and fibrinogen concentration was also not significantly different between the two groups. The MA (Maximum Amplitude) and Alpha angle indicating the functional efficiency of platelets and fibrinogen were also similar in the two groups [Table 1].

The mean chest tube output in the first 24 hours was significantly lower in group II patients who received 25 mg/kg of tranexamic acid (8.04 ± 8.89 vs 12.41 ± 19.23 ml/kg/24 hours, P = 0.03). The number of patients who received packed red cell transfusions were higher in group II [30.64% (n = 19) vs 14.51%(n = 9), P = 0.03]. There was no difference between the number of patients receiving FFP, platelet concentrates or cryoprecipitate between the two groups. There was no difference between the two groups in the volume of packed red cells used (9.21 ± 7.13 ml/kg in group II vs 12.41 ± 9.23 ml/kg in group I, P = 0.712). Similarly, the amount of FFP transfused did not significantly differ (13.91 ± 13.38 ml/kg in group II vs 11.02 ± 8.04 ml/kg in group I, P = 0.19). The volume of cryoprecipitate and platelet concentrates consumed were also similar between the two groups [Table 2]. None of the patients in either of the groups required re exploration for post-operative bleeding.

DISCUSSION
Post-operative bleeding is an expected complication in cyanotic patients undergoing congenital heart surgery. At our institute tranexamic acid is being used prophylactically as an antifibrinolytic agent to decrease perioperative bleeding in pediatric cardiac patients for more than a decade. The use of tranexamic acid in pediatric cardiac surgery has been marked by substantial variability in the dosing regimens followed by various cardiac centers. The proposed dose ranges in previous studies varies from 10 to 100 mg/kg. Additionally cardiac anesthesiologists have also demonstrated practice variations in using either a bolus dose, continuous infusion or a combination of both. Our institute has been following the triple dose regimen of tranexamic acid at 10 mg/kg as suggested in a randomized study by Chauhan et al. In another single center study, Giordano et al. had employed a bolus dose of 20 mg/kg after induction and after protamine demonstrating the efficacy of tranexamic acid in decreasing blood loss and transfusion needs during cardiac surgery in both cyanotic and acyanotic patients. We compared the standard dosing at our center to a higher dose of 25 mg/kg administered as a triple dose schedule to assess the possible superiority of a higher dose in further limiting post-operative blood loss within the margin of safety. We chose cyanotic patients exclusively as they form a vulnerable subset more prone to develop bleeding complications secondary to coagulopathies which are likely to coexist.

Our results showed that a higher dose of tranexamic acid at 25 mg/kg administered as a triple regimen after induction, in CPB prime and after protamine was superior to a lower dose of 10 mg/kg in minimizing post-operative blood loss. It is intuitive that the triple dose regimen is likely to compensate for the decreased plasma drug
levels that may result from hemodilution during CPB or volume resuscitation with crystalloids after weaning from CPB. Our results show that though the higher dose of tranexamic acid reduced blood loss, this did not translate to a reduction in perioperative transfusion requirements. Recently there have been attempts to identify the optimal target plasma concentration of tranexamic acid in inhibiting fibrinolysis. Fiechtner and Soslau have concluded that plasma concentration of tranexamic acid required to inhibit in vitro fibrinolysis is 10 mcg/ml and that to suppress plasmin-induced platelet activation is 16 mcg/ml.11,12 Fiechtner et al and soslau et al designed the optimal dose requirement of tranexamic acid during cardiac surgery as 5.4 mg/kg loading dose followed by 5 mg/kg/hr of infusion, with an additional 20 mg/L of CPB prime. He also found that the residual drug concentration at 12 hrs was higher in presence of renal dysfunction and would mandate a dose adjustment in this subset. Our lower dose regime was higher than this recommendation. Although in our study, the higher dose was associated with less drain output at 24 hrs, there was no clinically significant bleeding requiring additional blood products or re-exploration in the lower dose group as well. This indicates that the lower dose regime is probably adequate to prevent clinically significant fibrinolysis.

Contrary to our expectations, a larger proportion of patients in the high dose group required PRBC transfusion compared to the lower dose group without an associated increase in post operative blood loss. This could be due to the fact the transfusion practices were sometimes modified based on demands of the surgical team to target a higher hematocrit in cyanotic patients who had clinical evidence of hypovolemia in the early post operative period. Zhang et al in a retrospective single center study of 2026 patients, also showed a significant reduction of 12 hour and total post‑operative blood loss in patients who received tranexamic acid without a significant difference in allogeneic transfusion requirements.13 Our results also corroborate with existing evidence in favor of tranexamic acid in reducing post-operative blood loss.14,16 We surmise that our transfusion needs could also have been lowered with better standardization of policies related to

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Table 1: Preoperative and intraoperative data

| Parameter                      | Group I (10 mg/kg) | Group II (25 mg/kg) | P    |
|--------------------------------|--------------------|---------------------|------|
| Patient Characteristics        |                    |                     |      |
| Male gender (n,% )             | 31 (50)            | 31 (50)             | 0.99 |
| Age <1 month (n,% )            | 12 (21.3)          | 11 (17.7)           | 0.901|
| Age, 1 month-1 year (n,% )     | 21 (33.9)          | 22 (35.5)           |      |
| Age >1 year (n,% )             | 28 (45.2)          | 29 (46.8)           |      |
| Preoperative Data              |                    |                     |      |
| Redo surgery (n,% )            | 8 (12.6)           | 12 (19.4)           | 0.32 |
| Pre op HCT in % (mean±SD)      | 44.7±15.68         | 44.5±10.34          | 0.89 |
| Intraoperative data            |                    |                     |      |
| CPB time in min (mean±SD)      | 190.5±96.13        | 194.9±102.93        | 0.80 |
| ACC time in Min (mean±SD)      | 99.8±65.74         | 96.3±72.13          | 0.50 |
| Lowest CPB temperature in degrees (mean±SD) | 27.0±3.60  | 26.0±3.69  | 0.26 |
| Delayed sternal closure (n,% ) | 8 (12.9)           | 14 (22.5)           | 0.16 |
| TEG parameters                 |                    |                     |      |
| R time in min (mean±SD)        | 6.90±2.30          | 5.9±2.86            | 0.04 |
| K time in min (mean±SD)        | 3.52±1.33          | 3.3±2.16            | 0.49 |
| Alpha angle in degrees (mean±SD)| 52.3±11.03        | 53.3±16.62          | 0.68 |
| MA in mm (mean±SD)             | 53.3±11.30         | 54.3±16.53          | 0.70 |

(HCT= Hematocrit, CPB= Cardiopulmonary Bypass, ACC= Aortic cross clamp, TEG= Thromboelastogram, MA= Maximum Amplitude)

Table 2: Post operative blood loss and transfusion outcomes

| Parameter                      | Group I (10 mg/kg) | Group II (25 mg/kg) | P    |
|--------------------------------|--------------------|---------------------|------|
| Post operative blood loss at 24 hours in ml/kg (mean ± SD) | 12.4±19.23 | 8.04±8.89 | 0.03 |
| Blood and blood component usage |                    |                     |      |
| PRBC in ml/kg (mean±SD)        | 9.98±9.07          | 9.21±7.13           | 0.712|
| FFP in ml/kg (mean±SD)         | 11.02±8.04         | 13.9±13.38          | 0.192|
| Platelets in ml/kg (mean±SD)   | 10.90±6.9          | 9.03±6.76           | 0.144|
| Cryo ppt in ml/kg (mean±SD)    | 0.53±0.54          | 0.66±0.59           | 0.50 |
| Patients exposed to transfusion|                    |                     |      |
| PRBC (n,% )                    | 9 (14.5)           | 19 (30.64)          | 0.03 |
| FFP (n,% )                     | 53 (85.4)          | 44 (70.9)           | 0.06 |
| Platelet (n,% )                | 59 (95.1)          | 56 (90.3)           | 0.29 |
| Cryo ppt (n,% )                | 22 (35.4)          | 16 (25.6)           | 0.24 |

(PRBC= Packed red blood cells, FFP= Fresh Frozen Plasma)
perioperative transfusion thus limiting individual practice variations.

The major side effects of tranexamic acid that merits concern in the post-operative period include increased risk of seizures and renal complications. Our study investigated the safety of tranexamic acid with respect to occurrence of post-operative seizures and renal dysfunction requiring dialysis. Though none of the patients in the study cohort developed seizures, two patients in the lower dose group developed renal dysfunction as a sequelae of severe low cardiac output syndrome following myocardial dysfunction. The safety profile of tranexamic acid has been under close scrutiny especially in comparison to aprotinin. Pasquali et al. studied a large database of >20,000 pediatric patients undergoing cardiac surgery and found that use of tranexamic acid was associated with less mortality and bleeding requiring surgical re-intervention as compared to aprotinin in pediatric patients and in neonates. Martin et al. had identified a higher incidence of seizures in tranexamic acid group compared to Epsilon Amino Caproic Acid (EACA) group during open heart surgery (7.3% vs 3.3%, P = 0.019). Maeda et al. in a retrospective cohort study with propensity score analysis had identified a higher incidence of post-operative seizure with use of tranexamic acid (1.6% Vs 0.2%, difference 1.4%;95% CI, 1.0-1.9; P < 0.001). A recent metanalysis of 49 studies including 10,591 patients found tranexamic acid to be effective in reducing transfusion requirements in all kinds of cardiac surgery. They however cautioned that intravenous high dose tranexamic acid increased seizure risk by 4.83 times and advocated use of low dose continuous infusion for best results without increasing seizure risk.[1]

Our study is limited by the non-randomized design and small sample size. The lack of standardization of unit transfusion policies might have introduced bias which could have altered the transfusion practices on some occasions based on individual preferences. We also did not incorporate a continuous infusion following the bolus dose, into our regimen that is currently recommended based on the pharmacodynamic profile of the drug depicted in recent studies.[1]

CONCLUSION

In summary, tranexamic acid administered as an antifibrinolytic agent at a dose of 25 mg/kg in a triple dosing regimen after induction of anesthesia, in CPB prime and after protamine administration is more effective in minimizing post-operative blood loss than a lower dose of 10 mg/kg delivered as a triple dose method at the same time points during cardiac surgery. However, this was not accompanied by a parallel decrease in the amount of blood and blood components transfused during surgery. This dosing schedule was also not associated with significant renal dysfunction or post-operative seizures. Tranexamic acid could be a valuable adjunct in the perioperative care of cyanotic patients to decrease post-operative blood loss.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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