

Efficacy and Safety of Intraoperative Intravenous Tranexamic-acid in Neonates and Infants Weighing Less Than 5 kg Undergoing Congenital Cardiac Surgery: an Exploratory Retrospective Cohort Study

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Abstract

Background: Pediatric congenital heart diseases are associated with coagulation abnormalities, which are aggravated during cardiopulmonary bypass (CPB). There still have scarce information about the safety and efficacy of tranexamic acid (TXA) in neonates and infants' weight < 5 kg.

Objective: To determine the efficacy of intravenous TXA in neonates and infants' weight < 5 kg undergoing congenital cardiac surgery about postoperative blood loss, intra- and 24 hours postoperative transfusion, and postoperative morbidity/mortality.

Material and methods: A retrospective study was conducted between January 2015 and December 2021 in neonates and infants' weight < 5 kg undergoing congenital cardiac surgery under CPB. Patients with history of seizure, stroke, preoperative acute kidney injury, bleeding disorder, and who received TXA in the ICU were excluded. Patients were divided into the

controlled group (n=19) and the TXA group (n=103).

Results: TXA group had significant lower postoperative blood loss at 12 hours but not 24 hours postoperative allogeneic transfusion. Single bolus TXA > 30 mg/kg before incision tended to decrease postoperative bleeding at 12 hours ($b = -0.264$; $P=0.079$). High dose TXA > 50 mg/kg didn't increase the efficacy of TXA. TXA 60 and 82 mg/kg were associated with postoperative seizure and arterial thrombosis.

Conclusion: Intravenous TXA showed efficacy in decreasing postoperative blood loss at 12 hours but not 24 hours postoperative allogeneic transfusion. A high dose (> 50 mg/kg) of TXA did not increase its efficacy. The postoperative seizure was associated with high dose TXA. An optimal dose of TXA is warranted for further study.

Keywords: cardiac surgery, infant, neonate, seizure, tranexamic acid

Introduction

Pediatric congenital heart disease is usually associated with coagulation abnormalities from an immature hemostatic system; low levels of clotting factors inhibitor, and fibrinogen; and platelet dysfunction.¹ In particular, cyanotic congenital hearts have more coagulation abnormalities from liver and platelet dysfunctions, including decreased factors synthesis.² These abnormalities are more aggravated during cardiopulmonary bypass (CPB) due to exposure to heparin, foreign surfaces, hemodilution, and hypothermia. The result is platelet activation, abnormal coagulation, and decreases in platelet number/function and fibrinogen levels, including an increasing in fibrinolysis.³ All these factors, couple with the extensive suture line from surgery, raise the risk associated with pediatric cardiac surgery. Specifically, excessive intra- and postoperative bleeding are likely to occur, leading to allogeneic transfusion that increases postoperative morbidity and mortality.⁴

Following the suspension of aprotinin, tranexamic acid (TXA), a lysine analog is now the primary antifibrinolytic agent used in cardiac surgery. TXA has been reported to decrease postoperative blood loss in pediatric cardiac surgery^{5,6}, and blood loss, allogeneic transfusion and re-exploration in cyanotic pediatric cardiac surgery.⁷⁻¹³ TXA had thrombotic complications such as stroke, vascular thrombosis, myocardial infarction and acute kidney injury (AKI). Furthermore, TXA has neurological complications such as seizures, with a reported incidence of 1.6% in a TXA group vs 0.2% in a control group.¹⁴ All thrombotic and neurological complications can

substantially worsen postoperative outcomes. It is not yet clear whether the efficacy or safety of TXA depends on the dose and its mode of administration.

Chauhan and colleagues reported the results of a randomized trial of TXA in 150 cyanotic patients (aged 2 months-15 years; 5 groups) who underwent cardiac surgery. Their study showed that TXA given 3 times as a bolus of 10 mg/kg (after induction of anesthesia before incision, during CPB, and after protamine created the maximal benefit of decreasing postoperative blood loss and allogeneic transfusion. Then bolus 2 times of 20 mg/kg at induction and after protamine while given TXA of 50 mg/kg single bolus at the induction of anesthesia showed the least benefit but no complications (especially postoperative seizure).⁷

In another work, Hasegawa and coworkers performed bloodless pediatric cardiac surgery on patients weighing < 20 kg (n=20). They found that administering intravenous TXA (100 mg/kg) followed by an intravenous drip at a rate of 10 mg/kg/h decreased postoperative blood loss and resulted in significantly higher postoperative hemoglobin without any incidents of seizure.¹⁰ Additionally, a retrospective analysis of 4,883 adult cardiac surgical patients revealed that a moderate dose of TXA (24 mg/kg) had an incidence of seizure of 2.5% vs 1.2% for the control group.¹⁵ A previous study recommended that a high TXA dose should be given to cases with a high risk of bleeding during surgery, while a low TXA dose should be administered if the risk of bleeding was low. The researchers proposed that this approach maintained the safety profile while achieving maximal benefits.¹⁶

A large retrospective study conducted in pediatric patients aged between 31 days and 12 years who underwent simple cardiac surgery. The TXA technique employed was that an intravenous infusion (15 mg/kg) was given from the induction of anesthesia until the end of the surgery. This work presented that TXA decreased postoperative blood loss at 12 hours and total blood loss volume.⁶ This outcome was particularly the case for patients aged < 1 year, those with a body weight < 10 kg and cyanosis patients; however, it was not achieved when an allogeneic transfusion was involved. Nevertheless, Zhang and associates did not find any postoperative seizures, the major complication of TXA.⁶ A meta-analysis of antifibrinolytic agents in patients aged < 18 years reported the efficacy of TXA in reducing postoperative blood loss, they could not determine an optimal dose and technique.¹²

Despite more information about the efficacy and safety of TXA in adult cardiac surgery.¹⁵⁻¹⁷ Unfortunately, there was very little information about the use of TXA in small infants weighing less than 5 kg and in neonate patients undergoing complex cardiac surgery with a high risk of postoperative bleeding.¹⁸ In addition, with the difference in pharmacokinetic of TXA of adult, small infant and neonate¹⁹⁻²¹, the information in adult could not be used in these groups. This exploratory study aimed to determine the efficacy of intraoperative intravenous TXA in infants weighing less than 5 kg and neonates undergoing complex cardiac surgery (cardiopulmonary bypass) in terms of perioperative blood loss and 24-hours postoperative allogeneic transfusion. The study also explored the safety of TXA as indicated by the morbidity (seizure, vascular thrombosis,

stroke, AKI, and reoperation due to massive bleeding) and mortality as well as other outcomes (ventilator days, ICU and hospital length of stay, 30-days in-hospital mortality and optimal dose of TXA in this group of patients.

Materials and methods

This was a descriptive, observational, single-center-based study. We performed a retrospective review of the electronic medical records of 134 infants whose body weight was less than 5 kg and neonates (0-30 days) who underwent elective simple and complex cardiac surgery under CPB at Siriraj Hospital between January 2015 and December 2021. Patients with history of seizure, stroke, preoperative AKI, or pre-existing coagulation disorder, or those receiving antiplatelets or anticoagulants and TXA in the ICU postoperatively were excluded. This meant that 122 patients were eligible for the analysis. This study was approved by the Ethics Review Committee for Human Research, Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University (approval number Si530/2021).

The studied patients were divided into 2 groups. They were a “control group” (n=19, did not receive intraoperative intravenous TXA) and a “TXA group” (n=103, received intraoperative intravenous TXA). Generally, the technique of TXA administration at our institute was a slow bolus. Therefore, to derive more detail for the study’s analyses, the TXA group was subdivided into 2 groups. One was a “TXA single-dose group (TXA-S)” (the patients received only 1 dose of intraoperative intravenous TXA during surgery;

n=75). The other was a “TXA multiple-dose group (TXA-M)” (the patients received more than 1 dose of TXA during surgery; n=28).

All patients underwent standard anesthesia and surgical techniques for surgical repair of congenital heart disease. Systemic heparin (300 units/kg) and an additional dose were used to provide systemic anticoagulation (activated clotting time > 480 sec) during surgery. The CPB circuit was primed with a crystalloid and 20% albumin solution. Red blood cells (RBCs) were added to the CPB circuit to keep the hematocrit level between 24% and 39% in the palliative cyanotic cardiac surgery. To prevent fluid overload, extra fluid was removed by ultrafiltration either during or after separation from CPB. Protamine was administered at a protamine to heparin ratio of 1-1.2:1.

We collected patients’ demographic and clinical data (comorbidities, ASA classification, surgery type and duration, CPB and aortic cross-clamp times, prime volume, lowest temperature during CPB, deep hypothermic circulatory arrest, and amount of intraoperative intravenous TXA). The primary and secondary efficacy outcomes were also carefully recorded. The “primary efficacy outcome” of postoperative blood loss was represented by the pericardial and mediastinal fluid collected via drainage tube (DT) at 12 hours and the total postoperative blood loss (the total DT fluid volume measured before DT removal).

The “secondary efficacy outcome” was the total volume of intraoperative and 24-hour postoperative allogeneic transfusion (RBCs and blood components [fresh frozen plasma, cryoprecipitate, and platelets]). The threshold

for RBC transfusion was a hematocrit between 24% and 39% (in palliative cyanotic surgery) during CPB and 30% and 50% (in palliative cyanotic surgery) after the termination of CPB. The indications for fresh frozen plasma, cryoprecipitate, and concentrated platelets were based on coagulation test results and the clinical judgments of the attending anesthesiologists and cardiac surgeons.

The safety outcomes were assessed via postoperative morbidity and mortality. The data collected were the incidence and details of any postoperative seizure (until discharge from the hospital), stroke, AKI, vascular thrombosis, and reoperation due to massive bleeding (drainage rate >10% of estimated blood volume/h for 2 hours or if cardiac tamponade).⁶ The resource utilization (ventilator days and length of ICU and hospital stay) and a 30-days in-hospital mortality rate were also recorded.

This study used the following definition: 1) *Significant blood loss at 6 hours*: blood loss > 10% of a patient estimated blood volume within the first 6 postoperative hours¹⁸ 2) *reoperation due to massive bleeding* was performed when massive bleeding occurred with a drainage rate > 10% of the estimated blood volume/hour for 2 hours or if cardiac tamponade occurred⁶ 3) *stroke*: a new focal neurologic neurological deficit lasting > 24 hours or leading to earlier early death. It was confirmed by computed tomography (CT) or magnetic resonance imaging showing cerebral infarction or hemorrhage²² 4) *Seizure*: a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain that clinically manifested as tonic, clonic, or

myoclonic activity of the limb or trunk, or that was generalized all over the body with or without loss of awareness. The cause of the seizure was confirmed with either CT or magnetic resonance imaging and an electroencephalogram^{6,22,23}

5) *Myocardial infarction*: the development of pathological Q waves on 2 or more adjacent leads on an electrocardiogram change indicative of ischemia (ST-segment elevation or depression) on an electrocardiogram, or a change in serum troponin T²² 6) *Acute kidney injury (AKI)*: defined by the Acute Kidney Injury Network criteria such as AKI stage I when serum creatinine increase 1.5-1.9 time baseline^{22,23} 7) *Prolonged mechanical ventilation* was defined as postoperative mechanical ventilation lasting longer than 72 hours.⁶

Statistical analysis

The sample size was calculated using an incidence of seizures of 1.6% based on the work of Maeda et al, given allowable error 0.65, at the confidence level of 95%.¹⁴ We calculate the sample size of this study base on the formula $N = Z\alpha^2 pq / \Delta^2$ and obtained 122 as an approximate number of patients require of this study. With the additional of 10% drop out. So, the final sample size was 134 patients.

Normally distributed continuous variables are shown as mean and standard deviation. They were compared using a 2-sample t-test. Non-normally distributed continuous variables are shown as median and interquartile range and were compared using the Wilcoxon-Mann-Whitney test. Categorical variables are presented as the frequency and percentage; comparisons

were made using the chi-square squared or Fisher's exact test. A multiple linear regression model was used to analyze the effects of the TXA dose on the volume of blood loss and allogeneic transfusion. Since the volume of blood loss at 12 hours, total blood loss, and volume of allogeneic transfusion (packed-red-cell and blood-component transfusions) were positively skewed, log10 transformation was applied. The results are presented as linear regression coefficients (b) and *P*-values.

All statistical analyses were performed with IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, USA). All tests were 2-sided, and *P*-value < 0.05 was considered statistically significant.

Results

Patient characteristics and surgical data

The 122 studied patients consisted of 19 patients in the control group and 103 patients in the TXA group. Neonates represented 41% of the cohort study (50/122). Cyanosis patients accounted for 30% of the cohort (37/122); they represented 47.4% of the control group (9/19) and 27.2% of the TXA group (28/103). The patients' characteristics and their preoperative and surgical data are shown in Table 1. There was a higher incidence of surgery with complicated bleeding in the TXA group than in the control group including arterial switch operation, (10.7% vs 0%); and interrupted aortic arch, (5.8% vs 0%). Nevertheless, there were no statistically significant differences in the types of surgery between the two groups (*P*=0.083). Additionally, the number of cyanotic and neonatal patients in

Table 1 Patients' characteristics and surgical data

	Control group (n=19)	TXA group (n=103)	P-value
Male, n (%)	12 (63.2)	55 (53.4)	0.464
Age (days), median (IQR)	30 (12-120)	60 (15-180)	0.190
Body weight (kg), mean±SD	3.5±0.6	3.5±0.8	0.764
Height (cm), mean±SD	52.6±4.9	54.9±7.1	0.178
Body mass index (kg/m ²), mean±SD	12.7±2.0	11.9±2.5	0.174
Body surface area (m ²), median (IQR)	0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.630
Neonate, n (%)	10 (52.6)	40 (38.8)	0.314
ASA III, n (%)	8 (42.1)	60 (58.3)	0.217
ASA IV, n (%)	11 (57.9)	43 (41.7)	
Cyanosis, n (%)	9 (47.4)	28 (27.2)	0.103
Preoperative data			
Hemoglobin (gm/L), mean±SD	15.1±9.2	12.9±2.3	0.297
Hematocrit (%), mean±SD	37.5±5.8	37.8±5.4	0.845
Platelet (10 ⁹ /L), mean±SD	420.9±146.4	367.2±145.3	0.142
Prothrombin time (min), mean±SD	12.8±2.5	13.5±9.6	0.735
APTT, mean±SD	29.6±4.5	28.8±5.4	0.567
Baseline serum creatinine (mg/dL), mean±SD	0.4±0.2	0.3±0.2	0.350
Type of surgery, n (%)			
Arterial switch	0	11 (10.7)	
Norwood	2 (10.5)	6 (5.8)	
Truncus arteriosus	2 (10.5)	6 (5.8)	
Interrupted aortic arch	0	6 (5.8)	
TAPVR	2 (10.5)	8 (7.8)	
Atrioventricular septal defect	3 (15.8)	12 (11.7)	
Ventricular septal defect	3 (15.8)	23 (22.3)	
Atrial septal defect & CorTriatum	0	4 (3.9)	
MBTS under cardiopulmonary bypass	4 (21.1)	9 (8.7)	
Others	3 (15.8)	8 (7.8)	
Redo-surgery (re--sternotomy), n (%)	0	8 (7.8)	-
TXA dose (mg/kg), (min-max)	0	8.6-120.0	
TXA dose (mg/kg), median (IQR)	0	30.0 (12.1-40.0)	
Other TXA dose with iv drip 15 mg/kg/h, median (IQR)	0	45.0 (33.8-67.7)	

Table 1 Patients' characteristics and surgical data

	Control group (n=19)	TXA group (n=103)	P-value
Different TXA dose (compared to iv drip 15 mg/kg/h), median (IQR)	0	21.3 (6.3-40.6)	<0.001
Prime volume (ml/kg), median (IQR)	97.0 (83.9-136.8)	95.1 (75.3-132.8)	0.888
Prime volume/blood volume, median (IQR)	1.2 (1.0-1.7)	1.2 (0.9-1.7)	0.888
Cardiopulmonary bypass time (min), median (IQR)	78.0 (50.0-128.0)	96.0 (68.0-155.0)	0.169
Aortic cross-clamp time (min), median (IQR)	35.0 (0-63.0)	57.0 (32.0-99.0)	0.035
Lowest temp during cardiopulmonary bypass (°C), median (IQR)	32.2 (28.6-33.8)	29.3 (22.2-32.2)	0.076
Deep hypothermic circulatory arrest, n (%)	3 (15.8)	21 (20.4)	0.763
Surgical time (min), median (IQR)	140.0 (120.0-210.0)	180.0 (135.0-270.0)	0.100

Data are presented as n (%), median (interquartile range, IQR) and mean±SD. TXA,; tranexamic acid; ASA, American Society of Anesthesiologists physical status; MBTS, modified Blalock- Taussig shunt

each group did not differ significantly, while 7.7% of the TXA group were redo-surgeries. There were no significant differences in the prime volume, CPB and aortic cross clamp time, lowest temperature during CPB, incidence of deep hypothermic circulatory arrest (DHCA) and surgical time between the two groups.

Blood loss and transfusion outcomes

Compared with the control group, the TXA group had a significantly lower blood loss at 12 hours (8.7 (3.6-21.7) vs 16.2 (3.3-20.7), $P<0.001$) and a lower total blood loss volume/ estimated blood volume (0.1 ± 0.2 vs 0.4 ± 0.5 , $P=0.013$). However, there were no statistically significant differences in the overall blood loss, allogeneic transfusion and significant blood loss at 6 hours.

Postoperative outcomes

There were no statistically significant differences between the control group and the TXA groups regarding their highest serum creatinine

levels in the first 48 hours, the incidence of AKI, ventilator days, ICU and hospital lengths of stay, and 30-day mortality (Table 3). Three patients in the TXA group had post operative seizures. The first patient aged 79 days, weighing 4.2 kg, and undergoing aortopulmonary window repair, received TXA (TXA-M) at 60 mg/kg in multiple dose technique. The second patient, age 53 days, weighing 2.8 kg, and undergoing a right modified Blalock-Taussig shunt under CPB, received TXA (TXA-M) at 82 mg/kg in multiple dose technique. The CT scans of these two patients did not reveal any significant or ischemic patterns. Both patients responded well to anticonvulsant medications, and there was no mortality. The last patient 27 days old, weighing 2.7 kg, and undergoing a right modified Blalock-Taussig shunt under CPB-received TXA (TXA-S) at 9.6 mg/kg. A CT scan of this patient revealed cerebral venous sinus thrombosis, possibly arising from an infection;

Table 2 Blood loss and allogeneic transfusion

Blood loss and allogeneic transfusion	Control group (n=19)	TXA group (n=103)	<i>P</i> -value
Blood loss			
Significant blood loss at 6 h, n (%)	10 (52.6)	33 (32.0)	0.116
Significant bleed at 12 h, n (%)	13 (68.4)	54 (52.4)	0.221
Blood loss at 12 h/kg (ml), median (IQR)	16.2 (3.3-20.7)	8.7 (3.6-21.7)	<0.001
Blood loss all/kg (ml), median (IQR)	26.8 (12.8-50.0)	23.7 (12.5-48.3)	0.924
Blood loss all/blood volume, mean±SD	0.4±0.5	0.1±0.2	0.013
Allogeneic transfusion			
Red blood cell (OR and ICU) (ml/kg), median (IQR)	118.7 (88.1-176.9)	145.0 (97.1-194.3)	0.357
Blood component (OR and ICU) (ml/kg), median (IQR)	43.9 (0-73.2)	38.2 (13.9-92.5)	0.711
Re-sternotomy from massive bleeding, n (%)	0	4 (3.9)	–

Data are presented as n (%), median (interquartile range, IQR), and mean±SD. TXA, tranexamic acid; OR, operating room; ICU, intensive care unit

there was no mortality for this patient.

One patient in the TXA group, aged 125 days old, weighing 4.6 kg, and undergoing atrioventricular septal defect repair received TXA (TXA-M) at 60 mg/kg. This patient developed femoral artery thrombosis at the site of femoral artery catheter placement. In addition, 4 patients in the TXA group (4/103; 3.9%) underwent re-sternotomy due to massive bleeding.

Subgroup analysis (Table 4)

The technique of TXA administration in this study was a slow bolus ranging from 8.57 to 120.00 mg/kg. This dose was significantly lower than the dose of 15 mg/kg/h used in the study by Zhang et al (30.0 [12.1-40.0] vs 45.0 [33.8-67.7] mg/kg; $P<0.00$).⁶ Regarding the bleeding outcomes of the different TXA techniques, the TXA multiple-dose group (TXA-M) had a significantly higher

total TXA dose than the TXA single-dose group (TXA-S) (59.0 [33.6-63.5] vs 25.1 [10.7-31.4] mg/kg; $P<0.001$). However, these two groups did not have any significant differences in their blood loss volumes at 12 hours, total blood losses, allogeneic transfusion volumes, or postoperative outcomes. Two patients (7.7%) in the TXA multiple-dose group developed seizures, while one patient (1.3%) in the TXA single-dose group developed a seizure ($P=0.167$). In addition, one patient in the TXA multiple-dose group had thrombosis of the femoral artery at the site of femoral artery catheter placement.

Univariate analysis of the factors associated with postoperative blood loss and allogeneic transfusion (Table 5) revealed that higher postoperative blood losses and higher allogeneic transfusion volumes were associated with (1) a

Table 3 Postoperative outcomes

Postoperative outcomes	Control group (n=19)	TXA group (n=103)	P-value
Mortality at discharge, n (%)	1 (5.3)	7 (6.7)	0.938
Seizure	0	2 (normal CT scan) 1 (CT scan: cerebral venous thrombosis)	–
Highest serum creatinine in first 48 h, median (IQR)	0.4 (0.3-0.7)	0.3 (0.3-0.5)	0.429
Postoperative acute kidney injury, n (%)	3 (15.8)	20 (19.4)	0.498
Vascular thrombosis, n (%)	0	1 (thrombosis of femoral artery at site of placement)	
Ventilator day (days), median (IQR)	3.0 (3.0-7.0)	5.0 (2.0-7.0)	0.489
Prolonged mechanical ventilation, n (%)	9 (47.4)	65 (63.1)	0.212
ICU length of stay (days), median (IQR)	7.0 (5.0-11.0)	7.0 (4.0-13.0)	0.783
Hospital length of stay (days), median (IQR)	11.0 (8.0-23.0)	12.0 (7.0-19.5)	
Re-operation from massive bleeding, n (%)	0	4 (3.9)	–

Data are presented as n (%), and median (interquartile range, IQR). TXA, tranexamic acid; ICU, intensive care unit

high ASA physical status (ASA III-IV), (2) a CPB time > 90 min, (2) duration of surgery > 3 hours, (3) the lowest temperature during CPB of < 32°C, and (4) a high prime volume/blood volume. In contrast, cyanosis was only associated with a higher RBC transfusion volume.

After adjusting for confounders in a multiple linear regression analysis (Table 6), higher postoperative bleeding and allogeneic transfusion volumes were significantly associated with a high prime volume/blood volume ratio and the lowest temperature < 28°C during CPB. However, cyanosis was only significantly associated with higher RBC transfusion volumes. For intraopera-

tive intravenous TXA, a single TXA dose > 30 mg/kg tended to decrease postoperative bleeding at 12 hours ($b = -0.264$; $P=0.079$).

Discussion

The results of this study confirm the efficacy of intraoperative intravenous TXA in reducing postoperative blood loss at 12 hours and reducing the total blood loss volume/estimated blood volume in the first 24 hours. Nevertheless, TXA could not reduce the intraoperative and 24-hour postoperative allogeneic transfusion volumes. These findings are similar

Table 4 Subgroup analysis of cyanosis patients and multiple technique of TXA

Cyanosis patients			
	Non-cyanotic patients (n=37)	Cyanotic patients (n=85)	P-value
Significant blood loss at 6 h, n (%)	29 (34.1)	8 (21.6)	0.686
Significant bleed at 12 h, n (%)	46 (54.1)	21 (56.8)	0.845
Blood loss at 12 h (mL/kg), median (IQR)	8.6 (3.6-24.5)	16.7 (7.4-39.6)	0.049
Blood loss all (mL/kg), median (IQR)	21.3 (11.3-43.2)	38.7 (19.5-51.7)	0.100
Blood loss all/blood volume, mean±SD	0.17±0.07	0.50±0.62	0.138
RBC (OR and ICU) (mL/kg), median (IQR)	128.2 (92.9-177.0)	165.7 (131.6-228.6)	0.001
Blood component (OR and ICU) (mL/kg), median (IQR)	34.7 (13.2-74.1)	57.5 (15.9-138.6)	0.058
Bleeding outcome of different TXA techniques			
	TXA-pre (n=75)	TXA-multiple (n=28)	
TXA dose (min-max) mg/kg	8.6- 92.9	11.1- 120.0	
TXA dose (mg/kg), median (IQR)	25.1 (10.7-31.4)	59.0 (33.6-63.5)	<0.001
Blood loss at 12 h (mL/kg), median (IQR)	8.4 (3.6-19.9)	10.0 (4.4-24.8)	0.299
Blood loss all (mL/kg), median (IQR)	23.7 (12.0-47.8)	23.4 (12.6-49.4)	0.594
Red blood cell (OR and ICU) (mL/kg), median (IQR)	138.3 (97.3-202.6)	149.0 (96.8-169.0)	0.928
Blood component (OR and ICU) (mL/kg), median, IQR)	35.6 (18.2-92.8)	36.2 (9.0-75.4)	0.320
Postoperative acute kidney injury, n (%)	16 (21.1)	4 (14.8)	0.581
Seizure, n (%)	1 (1.3)	2 (7.7)	0.167
	CT scan: cerebral venous thrombosis	CT scan: nonsignificant	
Thrombosis	0	1 (thrombosis of femoral artery at the site of placement)	-
Ventilator day, median (IQR)	5.0 (2.0-7.8)	5.0 (3.0-6.0)	0.681

Table 4 Subgroup analysis of cyanosis patients and multiple technique of TXA

Bleeding outcome of different TXA techniques			
	TXA-pre (n=75)	TXA-multiple (n=28)	
ICU length of stay (days), median (IQR)	8.0 (4.0-16.0)	6.0 (4.0-13.0)	0.264
Hospital length of stay, median (IQR)	12.0 (7.8-22.3)	10.0 (-7.0-17.0)	0.165
Mortality, n (%)	6 (7.9)	1 (3.7)	0.673

Data are presented as n (%), mean±SD, and median (interquartile range, IQR). OR, operating room; ICU, intensive care unit; TXA-pre, tranexamic acid single dose; TXA-multiple, tranexamic acid multiple dose

to the earlier reports that intraoperative intravenous TXA effectively reduced postoperative bleeding but not allogeneic transfusion volumes.^{6-8,11-13} Our results also differ from those of an adult study that indicated that TXA decreased both postoperative blood loss and allogeneic transfusion volume.¹⁷ This difference might result from the small size of pediatric patients compared with the CPB circuit and priming volume^{4,5}, for which an allogeneic transfusion is always needed to maintain the hemoglobin level, oncotic pressure and to prevent coagulation defect. Most complex congenital surgeries require low temperature or deep hypothermic circulatory arrest during CPB. These conditions are associated with more bleeding. Additionally, several previous reports suggested that there were differences between the pharmacokinetics of the pediatric (especially neonates and infants) and adult populations.¹⁹⁻²¹

In our subgroup analysis, despite the multiple-dose TXA technique resulting in significantly higher doses of TXA, these elevated dose levels did not improve the efficacy of TXA in reducing postoperative blood loss and allogeneic transfusion. In contrast, more postoperative

complications were found in the TXA multiple-dose group. For example, two of these patients had postoperative TXA associated seizures, while another patient experienced thrombosis at the placement site of the femoral artery catheter. These results are closed to the effects of TXA in pediatric craniofacial surgery²⁴ and in a meta-analysis of adult cardiac surgeries which higher TXA doses failed to provide any additional decrease in postoperative bleeding.¹⁷ This higher dose was also associated with more postoperative complications especially postoperative seizure. Moreover, in the multivariate analysis adjusted for factors associated with postoperative bleeding and allogeneic transfusion, a single TXA dose exceeding 30 mg/kg tended to decrease postoperative bleeding at 12 hours. This result was closed to the meta-analysis of Heyne and coworkers that a single dose of TXA could provide reduce postoperative bleeding and was suggested to be used as a prophylaxis dose against intra- and post-operative bleeding.²⁵

Regarding the safety of TXA, there were no significant differences in the incidence of postoperative stroke, thrombosis, AKI, length of

Table 5 Univariate analysis of factors associated with postoperative bleeding and allogeneic transfusion

	n	Log PO bleeding at 12 h	P-value	Log PO bleeding all	P-value	Log op + ICU red blood cell	P-value	Log op + ICU blood component	P-value
		mean±SD		mean±SD		mean±SD		mean±SD	
ASA physical status									
III	70	0.9±0.6	0.029	1.3±0.4	0.001	2.1±0.2	<0.001	1.3±0.7	0.042
IV	52	0.6±0.3		1.5±0.4		2.2±0.2		1.6±0.7	
Cyanosis									
No	85	0.9±0.5	0.195	1.3±0.5	0.099	2.1±0.2	0.001	1.4±0.7	0.363
Yes	37	1.1±0.5		1.5±0.3		2.2±0.2		1.5±0.8	
Re-do surgery									
No	118	1.0±0.5	0.503	1.4±0.4	0.884	2.1±0.2	0.477	1.4±0.7	0.798
Yes	4	1.1±0.6		1.4±0.4		2.2±0.1		1.5±0.7	
CPB (min)									
< 90	60	0.8±0.5	0.001	1.2±0.4	<0.001	2.1±0.2	<0.001	1.1±0.7	<0.001
> 90	62	1.1±0.5		1.6±0.4		2.2±0.2		1.8±0.6	
T-surgery (h)									
< 3	66	0.8±0.5	<0.001	1.2±0.4	<0.001	2.1±0.2	<0.001	1.2±0.8	<0.001
> 3	56	1.2±0.5		1.6±0.4		2.2±0.2		1.8±0.5	
Lowest temp during CPB (°C)									
> 32	45	0.9±0.5	<0.001	1.2±0.3	<0.001	2.1±0.2	<0.001	1.1±0.8	<0.001
28-31	27	0.8±0.5		1.2±0.5		2.0±0.2		1.3±0.7	
< 28	50	1.2±0.5		1.6±0.3		2.3±0.2		1.9±0.4	
TXA (mg/kg)									
No	19	1.1±0.4	0.457	1.4±0.5	0.777	2.1±0.2	0.829	1.3±0.9	0.562
Pre < 30	48	0.9±0.6		1.4±0.5		2.1±0.2		1.6±0.6	
Pre > 30	28	0.9±0.6		1.3±0.4		2.2±0.2		1.4±0.8	
Multiple < 60	12	1.0±0.5		1.4±0.3		2.1±0.2		1.4±0.7	
Multiple > 60	16	1.1±0.6		1.4±0.4		2.2±0.2		1.5±0.8	
Prime volume/ Blood volume		r = 0.422	<0.001	r = 0.405	<0.001	r = 0.442	<0.017	r = 0.211	0.006

ASA, American Society of Anesthesiologists; CPB, cardiopulmonary bypass; T surgery, surgical time; temp, temperature; TXA, tranexamic acid; TXA-pre, single dose tranexamic acid; TXA-multiple, multiple dose tranexamic acid; op, intraoperative; ICU, intensive care unit

ICU and hospital stay, as well as 90-days mortality. We found three patients who had postoperative seizure in the TXA group with the over incidence of seizure of 2.5% which was higher than 0.9 % of reported overall seizure after cardiac surgery.¹⁵ Two of these patients whose CT scan showed non-ischemic pattern received the total

dose of TXA 60 mg/kg and 82 mg/kg which was considered as a high dose.¹⁷ The rest of the seizure patient whose CT scan reviewed cerebral venous thrombosis, possible from infection received TXA as a single slow bolus 9.7 mg/kg after induction of anesthesia. If we exclude this patient so the incidence of possible TXA associated

Table 6 Multiple linear regression analysis of factor factors associated with postoperative bleeding and allogeneic transfusion

	Log bleed at 12 h		Log bleed all		Log RBC (op + ICU)		Log blood com (op + ICU)	
	b	P-value	b	P-value	b	P-value	b	P-value
Cyanosis	0.004	0.964	0.048	0.532	0.090	0.014	0.069	0.584
Lowest temperature								
< 28°C	0.220	0.112	0.272	0.011	0.153	0.002	0.754	<0.001
28–31.9°C	-0.017	0.891	0.022	0.816	-0.028	0.294	0.153	0.327
CPB > 90 min	0.114	0.345	0.176	0.058	0.044	0.313	0.233	0.125
Prime volume (ml/kg)	0.352	<0.001	0.223	<0.001	0.121	0.001	-0.013	0.912
TXA (mg/kg)								
Pre ≤ 30	-0.149	0.256	-0.030	0.768	0.000	0.609	0.159	0.333
Pre > 30	-0.264	0.079	-0.139	0.227	0.006	0.998	-0.279	0.142
Multiple any doses	-0.080	0.585	-0.021	0.849	0.009	0.862	-0.195	0.286

RBC, red blood cell; blood com, blood component; op, operating room; ICU, intensive care unit; CPB, cardiopulmonary bypass, TXA-pre, tranexamic acid single dose; TXA multiple, tranexamic acid multiple.

seizure was 1.9% which was slightly higher than the incidence (1.6%) report of large propensity score matching of Japan National data base (n=7,478) in pediatric cardiac patients < 12 years old.¹⁴ Anyhow, our study did not report the dose and the technique of TXA administration.

With the question that bolus technique may be associated with more seizure as this technique may cause the increasing in TXA faster and higher and passing through the brain especially in neonate and young infant. In the large retrospective study, a continuous infusion of 15 mg/kg/h of TXA did not show the incidence of seizure despite the total dose of TXA was significantly higher than in our study.⁶ Along with the recent report in 60 high-risk bleeding pediatric patients underwent complex cardiac surgery, the use of TXA infusion 10 mg/kg/h, human fibrinogen and human prothrombin complex also did not show the incidence of postoperative seizure.¹⁷ In

addition, the use of TXA 50 mg/kg bolus at the beginning and end of CPB and 100 mg/ml of priming volume in prime fluid of CPB found the incidence of postoperative TXA associated seizure 3.5% that was higher than in this study.²⁶ Moreover, the different technique and dose of TXA from slow bolus of total dose 30-50 mg/kg and 10 mg/kg slow bolus plus infusion of 1 mg/kg/h in cyanotic pediatric patients demonstrated the reduction of postoperative bleeding without incidence of postoperative seizure.⁷

Despite no conclusion of optimal dose of TXA in pediatric cardiac surgery¹¹⁻¹³, a previous meta-analysis in adult cardiac patients reported that TXA could reduce perioperative blood loss, transfusion rate and reoperation rate.¹⁰ However, TXA was associated with a 3.21-folds increase in the risk of seizure. Either bolus alone or bolus with continuous technique was effective, an intravenous high-dose of TXA (> 10 mg/kg bolus

and 1 mg/kg/h infusion) or slow bolus alone (> 50 mg/kg) didn't further decrease the transfusion rate compared with low-dose but increased the risk of seizure by 4.83 times

Compared to this study that used only slow bolus technique found postoperative TXA associated seizure and thrombosis of artery in high dose TXA. Lesser dose of TXA in continuous intravenous infusion technique might be a safer technique while keeping the efficiency of TXA. However, an optimal dose of TXA in neonates and small infants are warrant for urgent further studies. At the meantime, the recommended dose by Gertler and coworkers²¹ that independently of age, 10 mg/kg TXA bolus then infusion of 10 mg/kg/h then 4 mg/kg in the prime then reduced to 4 mg/kg/h after the start of CPB to maintain TXA concentration above 20 mcg/ml that could inhibit fibrinolysis activity up to 80%.

Limitations

As this was a retrospective study, so the limitation of this study was no active surveillance for complications such as thrombosis, thromboembolism. However, active search was done in every studied record about the incidence of seizures that were significant complications and should be recorded.

Conclusion

This retrospective exploratory study in neonates and infants weight less than 5 kgs underwent congenital cardiac surgery under CPB

showed the efficacy of intraoperative intravenous TXA in reducing postoperative blood loss at 12 hours postoperative and ratio of 24 hours postoperative blood loss and total blood volume. TXA single dose > 30 mg/kg showed a high tendency to reduce postoperative blood loss at 12 hours. Incidence of postoperative TXA associated seizure was 1.6% in multiple bolus of TXA. Femoral artery thrombosis at the site of catheter placement was found in TXA dose 60 mg/kg. Continuous infusion of lower dose TXA might be a safer technique while keep the efficacy of TXA. Optimal dose and technique of intraoperative intravenous TXA in neonate and small infants are warrant for further studies.

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Conflicting interest

The authors declare no conflicts of interest regarding any aspect of this study.

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