Original Article

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The Effects of Different Doses of Tranexamic Acid Infusions on the Postoperative Outcomes of Pediatric Cardiovascular Surgery

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Abstract

Aim: There are still concerns about its benefits and possible risks in pediatric patients, as well as the dosage regimen, frequency, and form of tranexamic acid. In this study, the effects of different doses of tranexamic acid used in pediatric congenital heart surgery were investigated.

Methods: The study was conducted between August 1, 2020 and April 30, 2021, by screening patient files and hospital data systems. Accordingly, patients in Group TXA-10 and Group TXA-25 were continuously administered 10 mg/kg/hour and 25 mg/kg/hour tranexamic acid infusions, respectively, from the induction of anesthesia until their transfer to the intensive care unit. The groups were compared in terms of the amount of bleeding, blood products used, and postoperative complications.

Results: Thirty-five patients were included in Group TXA-10, and 36 patients were included in Group TXA-25. There was no statistical difference between the groups in terms of gender, weight, height, or presence of cyanotic heart disease. The median post-pump activated clotting time in Group TXA-10 was significantly longer than in Group TXA-25 (153 vs. 141.5 seconds, p=0.003). There was no significant difference between the groups also in terms of the amount of bleeding; the median erythrocyte transfusion amount was 50 ml in both groups. The amount of fresh frozen plasma and platelets that needed to be transfused in Group TXA-10 was higher than in Group TXA-25, albeit not significantly. There was no difference between the groups in terms of postoperative complication rates.

Conclusion: Tranexamic acid can be safely and effectively used in pediatric heart surgery cases with an infusion rate of 10 mg/kg/hour.

Keywords: Child, heart defects, congenital

Introduction

The use of excessive and different types of blood products due to increased bleeding during cardiac surgery has been associated with increased morbidity and mortality in patients diagnosed with congenital heart disease (1,2). Traditionally, the use of antifibrinolytic drugs has been one of the most effective strategies employed in reducing blood loss, particularly during and after cardiopulmonary bypass (CPB). Tranexamic acid is a synthetic lysine derivative that binds to lysine-binding sites in plasminogen and inhibits plasmin activation (3,4). Its effectiveness has been demonstrated in studies conducted with large samples of adult cardiac surgery patients. Furthermore, its use in pediatric cardiac surgery featuring different doses and applications has also become widespread in recent years (3,4).

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However, still concerns about its benefits and possible risks in pediatric patients, as well as about the dosage regimen, frequency, and method of use (5). In clinical practice, tranexamic acid is administered by either bolus or infusion or by bolus and infusion combined, and at various doses that vary from clinic to clinic. Only a few studies are available in the literature on the effects of these different dosage regimens and different frequencies and ways of use. The results of these limited studies revealed that the administration of tranexamic acid by infusion is more effective and safe compared with other ways of use (5-7).

In view of the foregoing, the objective of this study was to evaluate the effects of different tranexamic acid infusion doses on the amount of postoperative bleeding, blood/blood product use, and postoperative intensive care outcomes in patients younger than six months who underwent cardiovascular surgery with a diagnosis of congenital heart disease.

Materials and Methods

Compliance with Ethical Standards

The study was planned in accordance with the Declaration of Helsinki after obtaining the required approval from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital local ethics committee (number: 2020-21-14 and dated: 19.10.2020). Written and verbal consent were obtained from all participants.

Study Design

This study was conducted retrospectively with patients younger than six months old who underwent congenital heart surgery between August 1st, 2020, and April 30th, 2021, in the hospital where this study was conducted. The patients were divided into two groups according to the tranexamic acid infusion dosage, that is, 10 mg/kg/h (TXA-10) or 25 mg/kg/h (TXA-25), used from the beginning of the surgical procedure until the patients were transferred to the intensive care unit. The patients' age, gender, height and weight information, the name of the surgery they underwent, the presence of any syndrome, whether their heart disease was cyanotic or not, their hemoglobin, hematocrit, thrombocyte, activated partial thromboplastin time, prothrombin time, international normalized ratio values measured both during the preoperative and postoperative periods, duration of surgery, cross-clamp and pump times, use of blood and blood products during the surgery and in the first 24 hours after the surgery, amount of drainage in the first 24 hours after the surgery, the need for revision and peritoneal dialysis, and whether there was a seizure were recorded in the study form. The patients who were older than six months, did not undergo CPB, did not receive a tranexamic acid infusion, had previous renal failure, and whose records could not be reached were excluded from the study.

Surgical Procedure

Infants whose oral intake was discontinued in accordance with the guidelines (solid foods: 6 h, breast milk: 4 h, and clear liquids: 2 h) were monitored by electrocardiography, pulse oximetry, non-invasive blood pressure measurement, and near-infrared spectrometry in the operating room. No premedication was administered to the patient. Mask ventilation and orotracheal intubation were performed after the administration of 0.05 mg/kg midazolam, 1 mg/kg ketamine, 1 microgram/kg fentanyl, and 0.1 mg/kg rocuronium in anesthesia induction.

Tranexamic Acid Infusion

A bolus dose of 25 mg/kg tranexamic acid was administered to all patients after anesthesia induction and after the conclusion of CPB. Also, 25 mg/kg of tranexamic acid was added to the CPB prime solution as well. Patients in group TXA-10 and Group TXA-25 were continuously administered 10 mg/kg/hour and 25 mg/kg/hour tranexamic acid infusions, respectively, from the induction of anesthesia until their transfer to the intensive care unit.

Erythrocyte transfusion was performed if the hemoglobin level was <10 g/dL after the conclusion of CPB, fresh frozen plasma transfusion was performed based on the coagulation test results, and platelet transfusion was performed after the surgery at the surgeon's discretion. Mortality was defined as death that occurred in the first 30 days following the completion of the surgery in the hospital. However, morbidity was defined as having at least one of the following conditions: stroke, seizure, renal failure, development of deep venous thrombosis, use of extracorporeal membrane oxygenation, reoperation for bleeding, and dependence on long-term mechanical ventilation.

Stroke was defined as a new ongoing focal neurologic deficit and infarction or hemorrhage demonstrated by brain tomography or magnetic resonance imaging. The seizure was defined as an incipient neuropsychiatric disorder with increased motor activity or in an agitated or hyperactive state. Renal failure was defined as the need for peritoneal dialysis in the postoperative period. On the basis of the venous Doppler ultrasonography findings and clinical symptoms, deep venous thrombosis was diagnosed. Reoperation for bleeding was performed if tamponade developed due to bleeding or in the event of a drainage rate of more than 10% of the total blood volume per hour. Prolonged mechanical ventilation was defined as greater than or equal to 72 hours of mechanical ventilation (8). The results were analyzed statistically.

Statistical Analysis

Descriptive statistics were given as mean ± standard deviation and median, with minimum-maximum values for continuous variables depending on their distribution. Numbers and percentages were used as categorical variables. The normal distribution of the numerical variables was analyzed using the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests. The Independent Samples t-test was used to compare two independent groups where numerical variables had a normal distribution. The Mann-Whitney U test was used on variables that did not have a normal distribution. The Pearson chi-square and Fisher's exact tests were used to compare the differences between categorical variables. For statistical analysis, "Jamovi" project (2021), Jamovi (Version 2.2.2.0) (Computer Software) (Retrieved from https://www.jamovi.org) and JASP (version 0.16) (Retrieved from https://jasp-stats.org) were used. In all statistical analyses, the significance level (p-value) was set at 0.05.

Results

The demographic and clinical characteristics of the study groups are given in Table 1 and Figure 1. There were 35 and 36 patients in groups TXA-10 and TXA-25. The groups were similar in sex distribution, height and weight measurements, and the frequency of cyanotic congenital heart disease (Table 1).

The groups were similar considering the intraoperative features except for the post-pumping ACT value and the requirement for additional heparin use (Table 2).

The median post-pumping ACT values were significantly higher in Group TXA-10 than in Group TXA-25 (153 sec vs. 141.5 sec, p=0.003). Although there were no newborns with additional intraoperative heparin use in Group TXA-10, most of the newborns (91.7%) in Group TXA-25 required an additional heparin dose during the surgery (p<0.001). Other intraoperative features were similar between the groups (Table 2).

Table 3 presents the laboratory investigations during the preoperative, intraoperative, and postoperative periods. We detected no significant differences in the laboratory investigations between the groups.

In Group TXA-10, the amount of bleeding in the postoperative period was similar. The median amount of erythrocyte transfusion was 50 mL in both groups. Although more fresh frozen plasma and platelets were transfused to the newborns in Group TXA-10, the differences between the groups were insignificant (Table 4).

The postoperative outcomes in Group TXA-10 and Group TXA-25 are given in Table 5. The median lengths of hospital stay and intensive care unit were 18 and 14.5 days in Group TXA-10. These lengths were 18.5 and 12.5 days in Group TXA-25. The differences were insignificant. The mortality rates were 25.7% and 22.2% in Group TXA-10 and Group TXA-25 (Table 5).

Discussion

In this study, the effects of tranexamic acid infusion administered using different dose protocols, that is, 10 mg/kg/hour or 25 mg/kg/hour, on the amount of

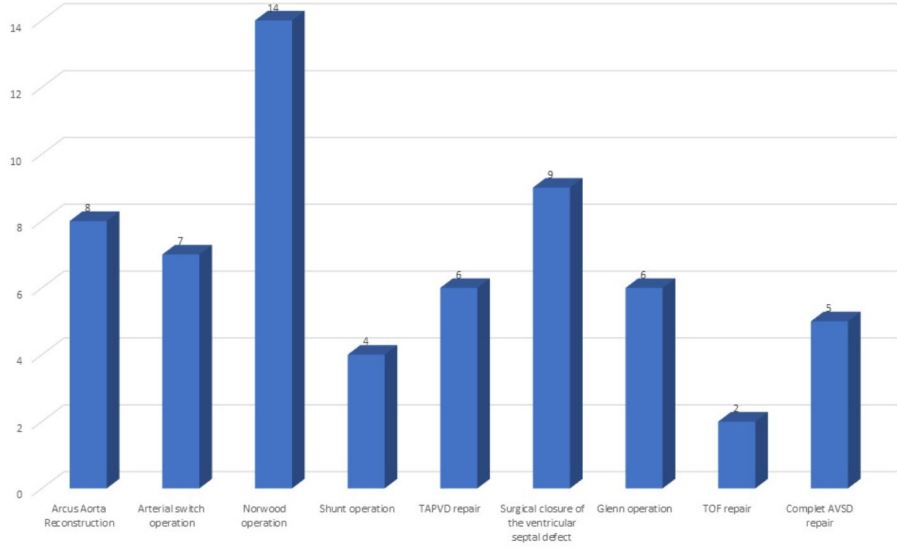

Figure 1. Types of operations performed in the cases atrioventricular septal defect (AVSD)

TAPVD: Total anomalous pulmonary venous drainage, TOF: Tetralogy of Fallot

postoperative bleeding, blood and blood product use, and postoperative intensive care outcomes were investigated. The study results revealed that both infusion strategies had similar effects on the amount of bleeding, blood product use, and complications observed while in the intensive care unit. To the best of the authors' knowledge, this study is one of the few conducted on the subject matter.

The development of coagulopathy following CPB may adversely affect the surgical results due to increased bleeding risk and hemodynamic instability. Different factors such as the prime solution used in CPB, the cardioplegic solution applied, the hemodilution, contact activation, thrombin and plasmin created by the fluids given in the perioperative period, and the consumption triggered by inflammation are effective in the development of coagulopathy. Anticoagulation agents such as unfractionated heparin, which are used in addition to coagulation, patient-specific conditions such as hypothermia, acidosis, and hypocalcemia may further increase the risk of bleeding (1-3). To prevent this situation,

Table 1. Demographic and clinical characteristics of the study groups

	Group TXA-10 (n=35)	Group TXA-25 (n=36)	p-value
Age (day)†	13.0 (3.0-70.0)	9.0 (3.0-66.0)	0.164*
Sex‡			
Female	14 (40.0)	15 (41.7)	0.999***
Male	21 (60.0)	21 (58.3)	
Height (cm)ɣ	50.7±3.6	50.1±3.3	0.443**
Weight (kg)ɣ	3.2±0.7	3.3±0.7	0.510**
Type of congenital heart disease‡			
Acyanotic	20 (57.1)	16 (44.4)	0.405***
Cyanotic	15 (42.9)	20 (55.6)	

†: Median (min-max), ‡: n (%), ɣ: mean ± standard deviation
*: Mann-Whitney U test
**: Independent samples t-test
***: Pearson chi-square or Fisher's exact test

Table 2. Comparison of the operative findings between the groups

	Group TXA-10 (n=35)	Group TXA-25 (n=36)	p-value
Time for surgery (min)†	250.0 (170.0-500.07	280.0 (150.0-420.0)	0.197*
Time for anesthesia (min)†	330.0 (240.0-600.0)	332.5 (190.0-480.0)	0.647*
Time for cardiopulmonary bypass (min)†	116.0 (59.0-300.0)	132.5 (34.0-259.0)	0.633*
Time for cross-clamping (min)†	71.0 (31.0-199.0)	80.0 (12.0-188.0)	0.618*
Activated coagulation time (sec)†			
Baseline	163.0 (102.0-600.0)	151.5 (93.0-248.0)	0.061*
Pre-pumping	600.0 (404.0-698.0)	600.0 (417.0-1000.0)	0.399*
Post-pumping	153.0 (119.0-261.0)	141.5 (50.0-185.0)	**0.003***
Total heparin dose (units)ɣ	1098.6±259.1	1144.4±238.1	0.440**
Additional heparin use‡	0 (0.0)	33 (91.7)	**<0.001*****
Additional heparin dose (units)†	-	1000.0 (750.0-1250.0)	-
Protamine dose†	1650.0 (900.0-3200.0)	1500.0 (200.0-2400.0)	0.713*
Intraoperative transfusions†			
Erythrocyte (mL)	40.0 (10.0-170.0)	50.0 (20.0-130.0)	0.339*
Fresh frosen plasma (mL)	10.0 (10.0-20.0)	10.0 (5.0-20.0)	0.617*
Platelet (mL)	20.0 (10.0-50.0)	30.0 (10.0-60.0)	0.217*
Cryoprecipitate (mL)	25.0 (17.0-50.0)	23.0 (17.0-32.0)	0.473*

†: Median (min-max), ‡: n (%), ɣ: mean ± standard deviation
*: Mann-Whitney U test
**: Independent samples t-test
***: Pearson chi-square or Fisher's exact test

Table 3. Laboratory investigations during the preoperative, intraoperative, and postoperative periods between the groups			
	Group TXA-10 (n=35)	**Group TXA-25 (n=36)**	**p-value**
Preoperative			
Hemoglobin (gr/dL)[ɣ]	12.7±1.7	13.1±2.2	0.440**
Hematocrit (%)[ɣ]	37.8±4.8	39.0±6.9	0.401**
Platelet count (10^9/L)[ɣ]	240.4±112.0	275.5±137.7	0.245**
aPTT (sec)[ɣ]	43.2±10.8	44.2±9.0	0.706**
INR[†]	1.3 (0.9-5.0)	1.3 (1.0-2.2)	0.913**
Post-pumping (in arterial blood gas sampling)			
Hemoglobin (gr/dL)[ɣ]	11.0±1.7	10.9±1.6	0.824**
Hematocrit (%)[ɣ]	33.8±5.5	33.5±4.9	0.788**
Postoperative (in the first arterial blood gas sampling)			
Hemoglobin (gr/dL)[ɣ]	11.9±1.7	12.2±1.9	0.477**
Hematocrit (%)[ɣ]	36.5±5.3	37.4±6.1	0.523**
Postoperative 12th hour			
Hemoglobin (gr/dL)[ɣ]	12.7±2.3	13.4±1.7	0.192**
Hematocrit (%)[ɣ]	37.2±6.7	38.7±4.6	0.269**
Platelet count (10^9/L)[†]	146.5 (29.0-421.0)	146.0 (40.0-808.0)	0.819*
INR[†]	1.4 (1.0-2.2)	1.3 (1.0-2.2)	0.124*

[†]: Median (min-max), [ɣ]: mean ± standard deviation
*: Mann-Whitney U test
**: Independent samples t-test

Table 4. Comparison of the postoperative bleeding and transfusion between the groups			
	Group TXA-10 (n=35)	**Group TXA-25 (n=36)**	**p*-value**
Postoperative bleeding (mL)[†]			
6th hour	40.0 [5.0. 175.0]	30.0 [5.0. 100.0]	0.623
12th hour	50.0 [5.0. 240.0]	50.0 [10.0. 130.0]	0.630
24th hour	70.0 [10.0. 325.0]	75.0 [25.0. 170.0]	0.986
Postoperative transfusions during the first 24 hour			
Erythrocyte (mL)[†]	50.0 [20.0. 285.0]	50.0 [10.0. 130.0]	0.810
Fresh frozen plasma (mL)[†]	75.0 [25.0. 160.0]	40.0 [10.0. 110.0]	0.286
Platelet (mL)[†]	210.0 [210.0. 210.0]	120.0 [120.0. 120.0]	0.317

[†]: median (min-max)
*: Mann-Whitney U test

the fibrinolytic system needs to be stabilized using aprotinin and lysine analogs such as epsilon-aminocaproic acid (EACA) and antifibrinolytic agents such as tranexamic acid (TXA). Today, the use of TXA has come to the fore as the use of aprotinin has been abolished due to marketing and safety concerns (9-14). However, although sufficient studies have been conducted on the use of TXA in adults, the studies on the use of TXA during pediatric cardiac surgery are limited.

There are controlled studies in which tranexamic acid was compared with placebo and other antifibrinolytic agents. The results of two different studies conducted with small samples with different cardiac pathologies indicated that the use of TXA reduces the use of blood products and is safe (13,14).

The data available in the literature on the effect of tranexamic acid on postoperative outcomes is contradictory. For instance, in a study involving children, Hasegawa et al. (7) reported that the inotrope usage and the peak lactate level in patients on TXA were lower than those of the control group, and they concluded that TXA improved clinical stability. They also reported that the TXA use shortened the extubation time and significantly reduced the length of stay in both the intensive care unit

Table 5. Postoperative outcomes in the study groups			
	Group TX-10 (n=35)	**Group TX-25 (n=36)**	**p-value**
Sternal closure‡			
No	29 (82.9)	25 (69.4)	0.296***
Yes	6 (17.1)	11 (30.6)	
Revisional surgery‡	29 (82.9)	25 (69.4)	0.296***
Reoperation for bleeding	1 (2.9)	1 (2.9)	0.999***
Length of hospital stay (day)†	18.0 (6.0-64.0)	18.5 (6.0-71.0)	0.734*
Length of intensive care unit (day)†	14.5 (4.0-64.0)	12.5 (4.0-66.0)	0.560*
Stroke	0	0	0.999***
Deep venous trombozis	0	0	0.999***
ECMO	2 (5.7)	1 (2.9)	0.620***
Peritoneal dialysis‡	1 (2.9)	1 (2.9)	0.999***
Postoperative urea (mg/dL)ɣ	20.5±8.4	20.9±8.0	0.819**
Postoperative creatinine (mgdL)ɣ	0.5±0.2	0.5±0.2	0.358**
Seiuzeres	1 (2.9)	1 (2.9)	0.999***
Outcome‡			
Survived	26 (74.3)	28 (77.8)	0.947***
Non-survived	9 (25.7)	8 (22.2)	

†: Median (min-max), ‡: n (%), ɣ: mean ± standard deviation
*: Mann-Whitney U test
**: Independent samples t-test
***: Pearson chi-square or Fisher's exact test

and hospital. In contrast, Zhang et al. (8) reported that TXA use neither affected the clinical situation significantly nor reduced the length of stay in the intensive care unit or hospital. A recently published meta-analysis including 15 randomized controlled trials including 1641 patients revealed that tranexamic acid is very effective for reducing blood loss in Chinese patients who have undergone pediatric heart surgery but is less effective for reducing the need for blood transfusions (9).

In comparison, in this study, TXA, an antifibrinolytic agent, was used in cardiovascular surgeries, in line with the standard clinical practice in the clinic where this study was conducted. The results of this study, taken together with the respective data reported in the literature, suggest that the use of TXA reduces the use of blood and blood products.

A wide range of TXA dosage regimens has been reported in the literature, from 10 to 100 mg/kg/hour administered by bolus and/or infusion (12). One reason for such a wide range is the lack of data on the effective dose in plasma caused by the fact that only a limited number of pharmacokinetic studies have been carried out on the subject matter (13,14). Zhang et al. (8) reported that they could use 15 mg/kg/hour TXA effectively and safely by infusion in pediatric cases. However, Grassin-Delyle et al. (14) stated that they obtained effective results when they used 10 mg/kg/hour TXA by infusion. In another study, TXA was administered at a dose of 25 mg/kg in a triple dose regime and compared with a lower dose of 10 mg/kg in cyanotic patients who underwent pediatric cardiac surgery; 25 mg/kg in a triple dose regime was associated with lower post-op blood loss without having major side effects (10). In comparison, in this study, both 10 mg/kg/hour and 25 mg/kg/hour doses of TXA were used safely.

Several side effects of tranexamic acid, including an increased risk of seizures in particular, have been mentioned in several studies. In one of these studies, Maeda et al. (15) stated that the frequency of seizures in patients who were administered TXA was eight times higher than that of other patients (1.6% vs. 0.2%). In another study conducted with 2026 cases, which also included the pediatric population, it was stated that the use of TXA caused no seizures (8). In comparison, in this study, seizures were observed in one patient in each group.

Another important side effect reported with the use of TXA is the risk of developing acute renal failure. Accordingly, in one study, it was reported that peritoneal dialysis was needed in only one case out of the 970 cases that were administered TXA (10). In comparison, in this study, peritoneal dialysis was needed in one patient in each

group, which refers to a higher incidence of renal failure compared to the abovementioned study. The fact that the age group covered in this study was younger and that the surgical complexity of the cases included in this study was higher might be the reason for the said discrepancy.

Other reported side effects were deep vein thrombosis and stroke (3-7), which were not observed in this study in any group.

Study limitations

The primary limitation of this study is that it was conducted as a single-center retrospective study with a limited number of cases. Secondly, there was no control group. However, it was possible to deduce an idea about efficacy and safety by comparing the study data with the relevant data in the literature. Thirdly, the plasma tranexamic acid levels of the cases were not studied. The strength of this study is that it was performed in neonatal and infant patients, and a similar CPB protocol was used in all patients.

Conclusion

Tranexamic acid can be used safely and effectively in cases of pediatric cardiac surgery. There was no significant difference between the study groups created on the basis of the doses of tranexamic acid administered by infusion in the amount and rate of bleeding, the number and number of blood products used, or the frequency of complications observed while in the intensive care unit. Multicenter studies to be conducted with larger samples are needed to verify the findings of this study.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital local ethics committee (number: 2020-21-14 and dated: 19.10.2020).

Informed Consent: Written and verbal consent were obtained from all participants.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Design: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Data Collection and/or Processing: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Analysis and/or Interpretation: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Literature Research: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Writing: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H.

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