Tranexamic Acid Therapy in Pediatric Cardiac Surgery: A Single-Center Study

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Tranexamic Acid Therapy in Pediatric Cardiac Surgery: A Single-Center Study

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Background. **We conducted a retrospective study of cyanotic and acyanotic patients undergoing cardiopulmonary bypass to determine the effect of tranexamic acid on blood loss and blood products administered during the operation in pediatric cardiac surgery.**

Methods. **From January 2008 to December 2011, during 2 different periods, a total of 231 pediatric patients undergoing cardiac surgery with cardiopulmonary bypass (123 cyanotic, 108 acyanotic) were included in this study. A total of 104 patients were in the antifibrinolytic group and exclusively treated with tranexamic acid that was given as a bolus of 20 mg/kg^{-1} after anesthetic induction and 20 mg/kg^{-1} after protamine. The other 127 patients were in the control group. We analyzed intraoperative and postoperative outcomes of tranexamic acid administration.**

Results. **There were no differences in mortality or operative time, but blood loss in 48 hours was greater in the control group ($p = 0.0012$). A significant difference was found in the amount of intraoperative erythrocyte concentrate transfused (140 ± 55 vs 170 ± 78 mL, $p = 0.0011$) but not in number. The number and amount of erythrocyte concentrate transfused in the first 48 postoperative hours were also greater in the control group (45 vs 77 patients, $p = 0.012$; 100 ± 40 vs 120 ± 55 mL, $p = 0.0022$). There were not many differences in the effect of tranexamic acid between the cyanotic and acyanotic subgroup.**

Conclusions. **This retrospective study provides evidence that tranexamic acid may be used in the field of congenital cardiac surgery effectively.**

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Open heart surgery in children with congenital heart disease often results in coagulation disturbances that may lead to intraoperative and postoperative loss of blood [1]. As transfusion of homologous blood components is associated with infectious and immunologic risks as well as increased mortality, blood-saving strategies are essential to reduce the amount of homologous blood used.

The use of antifibrinolytic agents to reduce blood loss after pediatric cardiac surgery has been described in several studies [1–11]. Tranexamic acid (TXA), an analog of the amino acid lysine, is an antifibrinolytic agent that competes with plasminogen for binding sites on fibrin and also prevents plasmin-induced platelet activation [12]. Although the presence of cyanosis would be associated with more bleeding episodes due to collateral vessel formation and platelet dysfunction caused by erythrocytosis [13], it is unclear whether there is a difference in the effects of TXA in cyanotic and acyanotic patients. We conducted a retrospective study of cyanotic and acyanotic patients undergoing cardiopulmonary bypass to determine the effect of TXA on blood loss and blood products administered during the operation in pediatric cardiac surgery.

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Material and Methods

Patient Selection

The data used in this retrospective study were collected at our center during 2 different periods. Ethical committee approval was gained from the Ethics Committee of the University of Naples Federico II. The Institutional Review Board had approved the use of databases for research. All participants were younger than 18 years of age and each legal guardian had preliminarily granted permission for the use of their medical records for research purposes. Children younger than 18 years of age who were scheduled to undergo elective cardiac surgery with cardiopulmonary bypass (CPB) between January 2008 and December 2011 were considered potentially eligible for inclusion in the study.

The control group included patients who underwent surgery between January 2008 and December 2009. During this period no antifibrinolytic agent was used. The tranexamic acid group was comprised of children operated between January 2010 and December 2011. From then onward, all patients were exclusively treated with

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tranexamic acid that was given as a bolus of 20 mg/kg^{-1} of TXA after anesthetic induction and 20 mg/kg^{-1} after protamine, as advocated by Chauhan and colleagues [5].

Neonates of less than 1 month of age, on mechanical ventilation preoperatively, and on inotropic support before surgery, were excluded from the study. Other exclusion criteria were a preexisting coagulation disorder, minimally invasive surgery, obvious kidney or liver disease, and known allergy to TXA. We included patients with preoperative anticoagulation therapy, such as administration of warfarin, aspirin, and ticlopidine. In our basic strategy, patients are requested to cease all anticoagulants 7 days before surgery [14].

Perioperative Management of Patients

All other parameters that may influence the perioperative management, in particular anesthesia and CPB course, were not modified during the 2 periods under review. All patients were operated upon by a surgical team of 3 surgeons. The following laboratory parameters were measured preoperatively, immediately after surgery, and 24 hours later: partial thromboplastin time (PTT), Quick, fibrinogen, platelets account, and serum creatinine. The transfusion amounts of erythrocyte concentrate, fresh frozen plasma, and platelets were determined for the operative period and the first 48 postoperative hours. Blood loss through the drains was defined as the amount of blood lost through the thoracic drains 48 hours after surgery. The anesthesiologists were responsible for intraoperative fluid management. Left atrial pressure or central venous pressure was maintained at 8 to 12 mm Hg to keep preload.

Postoperative care was undertaken by a team of intensivists who were blinded to the study groups and who managed bleeding and blood product administration according to existing protocols. Packed red cells were used for transfusion if the hemoglobin fell below 11 g/dL, although a clear-cut trigger of transfusion was not defined in this study. Fresh frozen plasma was used if the hemoglobin was above 11 g/dL and the patients clotting factors were considered based on the results of coagulation tests. Platelet concentrates were used in a dose of 1 unit (50 mL) per 10 kg, and 5% albumin was used for volume replacement if no active bleeding was present. Aristotle score comprehensive [15] was used to compare the complexity of procedures between the 2 groups.

Statistical Analysis

Continuous data are presented as mean ± SD. We compared clinical variables between the 2 groups by means of the nonparametric Mann-Whitney *U* test (for continuous variables) or the χ^2 and Fisher exact tests (for categoric variables). A *p* value of less than 0.05 was considered statistically significant. Data were analyzed by means of Statistica 6.0 software (StatSoft, Inc, Tulsa, OK).

Table 1. Demographic and Preoperative Data Between the TXA and Control Groups

Patient Characteristics	TXA Group (n = 104)	Control Group (n = 127)	*p* Value
Age (months)	37.5 ± 9.2	35.3 ± 11.4	0.11
Gender (male)	61 (58.6%)	69 (54.3%)	0.59
Weight (Kg)	11.1 ± 2.5	10.5 ± 2.8	0.09
BSA (m^2)	0.49 ± 0.15	0.46 ± 0.13	0.10
Repeat sternotomy	37 (35.4%)	38 (30.3%)	0.44
Aristotle score	8.6 ± 2.3	9.1 ± 2.7	0.13
Hemoglobin (g/dL)	12.9 ± 0.7	13.1 ± 1.3	0.16
Creatinine (mg/dL)	0.37 ± 0.2	0.42 ± 0.2	0.07
aPTT (seconds)	38.5 ± 6.5	40.3 ± 8.1	0.07
Quick (%)	89.4 ± 4.4	90.5 ± 5.2	0.09
Fibrinogen (mg/dL)	287 ± 41	265 ± 35	<0.0001
ATIII (%)	95 ± 11	93 ± 12	0.19
Platelets (×10^3/mL)	266 ± 60	283 ± 79	0.07

aPTT = activated partial thromboplastin time; ATIII = antithrombin III; BSA = body surface area; Quick (%) = prothrombin activity (normal value 70 to 130); TXA = tranexamic acid.

Results

Perioperative Parameters

In this study we included 231 patients; 104 in TXA group and 127 in the control group. There was no difference between the TXA group and control group (Table 1) except for the preoperative values of fibrinogen; however, the levels of this variable were within normal range.

The intraoperative and postoperative parameters (Table 2) were not different for mortality or operative time, but the blood loss in 48 hours was greater in the control group (187 ± 85 vs 225 ± 90 mL, respectively, $p = 0.0012$). No complications in the form of renal problems or cerebral events were noted in any of the children studied. There were only 2 patients requiring reexploration of the chest for bleeding, both in the control group.

Required Blood Products

Blood products were required by 65 patients (63%) in the TXA group and 91 patients (72%) in the control group ($p = 0.18$). Considering the intraoperative and postoperative (48-hour) requirements for blood products (Table 3), no significant difference was found in the number and amount of platelets concentrate or fresh frozen plasma transfused. A significant difference was found in the amount of intraoperative erythrocyte concentrate transfused (140 ± 55 [TXA group]) vs 170 ± 78 mL [control group], $p = 0.0011$) but not in number (60 vs 84 patients, $p = 0.23$) and in the number and amount of erythrocyte concentrate transfused in the first 48 postoperative hours (45 vs 77 patients, $p = 0.012$; 100 ± 40 vs 120 ± 55 mL, $p = 0.0022$).

Postoperative coagulation parameters were notable for the increased PTT values in both groups, with greater difference in the control group (45 ± 21 vs 54 ± 18, $p = 0.0005$) (Table 4). The activated partial thromboplastin

Table 2. Intraoperative and Postoperative Parameters

Variable	TXA Group	Control Group	*p* Value
Mortality within the first 30 days	2	3	0.59
Total operation time (minutes)	293 ± 62	311 ± 88	0.08
CPB time (minutes)	93 ± 33	100 ± 39	0.14
Aortic clamp time (minutes)	64 ± 22	69 ± 21	0.08
CPB temperature (°C)	29.5 ± 2	30 ± 2	0.06
Early reoperation for bleeding	0	2	0.3
Intubation time (hours)	22 ± 13	24 ± 15	0.28
ICU stay (hours)	76 ± 34	81 ± 41	0.32
Total blood loss (in 48 hours) (mL)	187 ± 85	225 ± 90	0.0012
Relative blood loss (in 48 hours) (mL/kg)	18 ± 7.5	21 ± 8.1	0.0019
Creatinine (mg/dL)	0.5 ± 0.2	0.54 ± 0.2	0.13
Fluid balance (in 48 hours) (mL)	−355 ± 170	−320 ± 190	0.14

CPB = cardiopulmonary bypass; ICU = intensive care unit; TXA = tranexamic acid.

time of the control group decreased with time, but was still significantly higher 24 hours after intervention, as compared with the TXA group (37 ± 10 vs 41 ± 12, $p = 0.007$).

Subgroup Analysis

The subgroup of children cyanotic and acyanotic was analyzed separately (Table 5). There was just a significantly higher amount (intraoperative) and number (postoperative) of erythrocyte concentrate used in the control cyanotic group ($p = 0.047$ and $p = 0.03$). Then, there was a significantly higher intraoperative amount of platelets concentrate transfused in the control acyanotic patients, but the number of patients was very small.

Comment

Excessive bleeding leads to increases in morbidity and mortality in adults [16] and children [17] after cardiac surgery with cardiopulmonary bypass. Excessive bleeding in children can be as much as 110 mL · kg^{-1} · 24 $hours^{-1}$ [18], blood transfusion may become necessary, and allogeneic blood transfusion may increase mortality [19]. Although major causes of postoperative bleeding in pediatric cardiac surgery are thrombocytopenia, platelet dysfunction, and hemodilution, one possible cause is increased fibrinolysis during CPB [20, 21], which occurs in about 16% of patients [22]. Moreover, congenital heart disease itself in pediatric patients has been shown to be associated with fibrinolysis [22, 23].

We conducted a retrospective study to assess the benefit of TXA in pediatric cardiac surgery in a single-center population, with a good number of participants (231 patients) in relation to the literature, in which cyanotic (123) and acyanotic (108) patients were discretely balanced (1:13 ratio). Neonates of less than 1 month of age were excluded from this study because for them coagulation disorders are known to be much stronger than in other age groups [10].

In this study, TXA significantly reduced blood loss and reduced intraoperative and postoperative amount and number of erythrocyte concentrate transfused (only postoperative), but it did not alter the amount of other blood products administered. We found a few statistical differences in the effect of TXA treatment in cyanotic and acyanotic patients. The results obtained in the literature for postoperative blood loss and other outcomes are generally heterogeneous and no clear results could be interpreted.

All previous studies were, as ours, single-center studies. Of these earlier studies, 2 were double-blinded

Table 3. Amounts of Blood Products Administered During and for 48 Hours After the Operation

Variable	TXA Group	Control Group	*p* Value
Transfusion	65 (63%)	91 (72%)	0.18
Blood products intraoperative (mL)			
Erythrocyte concentrate	140 ± 55 (n = 60)	170 ± 78 (n = 84)	0.0011 (0.23)
Platelet concentrate	40 ± 11 (n = 4)	50 ± 10 (n = 5)	0.19 (0.62)
FFP	120 ± 65 (n = 57)	110 ± 70 (n = 65)	0.26 (0.67)
Blood products within the first 48 hours (mL)			
Erythrocyte concentrate	100 ± 40 (n = 45)	120 ± 55 (n = 77)	0.0022 (0.012)
Platelet concentrate	50 ± 11 (n = 4)	50 ± 20 (n = 5)	1.0 (0.62)
FFP	90 ± 55 (n = 55)	100 ± 50 (n = 74)	0.14 (0.49)

FFP = fresh frozen plasma; TXA = tranexamic acid.

Table 4. Postoperative Coagulation Parameters

Variable	TXA Group	Control Group	*p* Value
Immediately postoperative			
aPTT (s)	45 ± 21	54 ± 18	0.0005
Quick (%)	57 ± 13	55 ± 10	0.18
Fibrinogen (mg/dL)	140 ± 56	153 ± 62	0.09
Platelets (×103/mL)	130 ± 39	120 ± 44	0.07
24-hours postoperative			
aPTT (s)	37 ± 10	41 ± 12	0.007
Quick (%)	70 ± 15	68 ± 13	0.27
Fibrinogen (mg/dL)	225 ± 65	240 ± 73	0.10
Platelets ($\times 10^3$/mL)	165 ± 42	155 ± 55	0.12

aPTT = activated partial thromboplastin time; Quick (%) = prothrombin activity (normal value 70 to 130); TXA = tranexamic acid.

studies [7, 9] that showed negative effects of TXA on both bleeding and amount of transfusion products required.

The study by Bulutcu and colleagues [3], which included 50 children and in which anesthesiologist and perfusionist were not blinded to patients' allocation, showed that TXA was effective in terms of both blood loss and transfusion. Three studies conducted by the same group (Chauhan and colleagues [4–6]) showed TXA had desirable effects. Nevertheless they included relatively large numbers of patients while other studies had fewer than 100 participants. The proportion of cyanotic patients varied among these earlier studies. Three studies included cyanotic and acyanotic patients with congenital heart disease [7–9] but 2 of these failed to show any TXA benefit [7, 9]. Moreover, 4 recent studies [3–6] that included all cyanotic patients have shown TXA beneficial effects. A recent randomized study [10] demonstrated the reduction in blood loss in pediatric cardiac surgery with no statistical difference on TXA effect in each cyanotic and acyanotic subgroup [10].

There is a large variation (10 to 100 mg/kg, bolus or continuous infusion) in the recommended dose in pediatric cardiac surgery [3–11]. In our study we practiced a bolus of 20 mg/kg^{-1} of TXA after anesthetic induction and 20 mg/kg^{-1} after protamine, as advocated by Chauhan and colleagues [5].

As the authors wrote, the variability in the dosage schemes used in the different studies is striking.

Moreover, the choice of TXA dosage was empirical based on its effects on blood loss and not on pharmacokinetic data regarding the fibrinolytic inhibiting activity of the drug. Data concerning the relationship between the dose of TXA and the appearance of adverse effects are not available in the literature, but we could suppose that the risk of side effects could be dose dependent, and high doses of TXA could probably increase the risk of adverse effect. In fact, the children's dose schemes are clearly extrapolated from adult studies.

In our study we had no complications related to the administration of TXA. In the pediatric population, side effects related to TXA administration are not well established. Most of the studies available have evaluated the effect on bleeding and blood product requirements, but none were designed to evaluate postoperative outcomes

Table 5. Difference Between TXA Group and Control Group in Cyanotic and Acyanotic Patients

	Cyanotic			Acyanotic		
Variable	TXA (n = 55)	Control (n = 68)	*p* Value	TXA (n = 49)	Control (n = 59)	*p* Value
Age (months)	37 ± 8.9	35.1 ± 10.8	0.29	37.3 ± 9.4	35.5 ± 11.5	0.38
Weight (kg)	11.5 ± 2.2	10.8 ± 2.5	0.10	11.1 ± 2.4	10.5 ± 2.3	0.18
BSA	0.48 ± 0.13	0.47 ± 0.12	0.65	0.48 ± 0.16	0.47 ± 0.13	0.72
Aristotle score	8.9 ± 2	9.5 ± 2.2	0.06	8.1 ± 1.8	8.5 ± 2.9	0.40
BP intraoperative (mL)						
EC	144 ± 58	177 ± 82	0.047	135 ± 50	160 ± 70	0.12
	(n = 34)	(n = 48)	(0.40)	(n = 26)	(n = 36)	(0.52)
PC	50	56.6 ± 5.7	0.22	30	40	0.009
	(n = 2)	(n = 3)	(0.80)	(n = 2)	(n = 2)	(0.74)
FFP	113 ± 70	107 ± 65	0.72	125 ± 80	120 ± 78	0.81
	(n = 27)	(n = 37)	(0.68)	(n = 30)	(n = 27)	(0.15)
BP after 48 hours (mL)						
EC	107 ± 45	125 ± 60	0.23	95 ± 35	114 ± 50	0.11
	(n = 21)	(n = 40)	(0.03)	(n = 24)	(n = 37)	(0.21)
PC	60	56 ± 23	0.35	40	40 ± 14	1
	(n = 2)	(n = 3)	(0.08)	(n = 2)	(n = 2)	(0.74)
FFP	95 ± 60	110 ± 55	0.29	80 ± 48	95 ± 45	0.21
	(n = 31)	(n = 35)	(0.71)	(n = 24)	(n = 39)	(0.10)

BP = blood products; BSA: body surface area; EC = erythrocyte concentrate; FFP = fresh frozen plasma; PC = platelet concentrate; TXA = tranexamic acid.

in the population. Actually, only 2 retrospective cohort studies [24, 25] reported side effects related to TXA administration during pediatric cardiac surgery. They found 9.6% renal injury, 1.8% renal failure, 3.5% seizure, and 2.6% other neurologic events. According to their results, more than 500 patients per group are needed to evaluate side effects related to TXA administration.

Study Limitations

The retrospective design of this study naturally impedes inference of possible causalities. An historical control group is utilized but alterations and improvements in the surgical procedures and perioperative environment between the 2 periods can obviously not be ruled out. We also excluded the neonatal population. Accordingly, a large, multicenter, randomized controlled trial with established doses is warranted to validate the efficacy of TXA in comparison with placebo or other antifibrinolytic drugs.

Conclusions

In conclusion, the data in this retrospective study provide further evidence that the TXA may be used as an antifibrinolytic substance in the field of congenital cardiac surgery with positive effectiveness, but the results of this study raise no consistent concerns regarding the safety. There were not many differences in the effects of TXA treatment in cyanotic and acyanotic patients.

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