Tranexamic Acid as a Means of Reducing the Need for Blood and Blood Component Therapy in Children Undergoing Open Heart Surgery for Congenital Cyanotic Heart Disease

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Abstract

Children undergoing cardiac operations using cardiopulmonary bypass (CPB) are at risk of significant postoperative bleeding and the need for transfusion. The antifibrinolytic drug, tranexamic acid, decreases blood loss in adult patients undergoing cardiac surgery. However, its efficacy has not been extensively studied in patients with cyanotic congenital heart defects (CHD). Using a prospective, randomized, double-blind study design, we examined 67 children undergoing repair of cyanotic CHD. After induction of anesthesia and prior to skin incision, patients received 15 mg/kg of tranexamic acid intravenously. At the end of CPB, a second bolus of tranexamic acid (15 mg/kg) or saline placebo was administered. Postoperative blood loss and transfusion requirements from the period after protamine administration until 24 hours after admission to the intensive care unit were recorded. In addition, the hematocrit, platelet count and other indices of coagulation were recorded every 6 hours. There was no significant difference in postoperative blood loss between the treated and the placebo group (12.51 $\pm$ 13.20 ml/kg per 24 hours, in the tranexamic acid group, *vs* 10.68 $\pm$ 6.38 ml/kg per 24 hours, in the placebo group). Also there was no significant difference in the amounts of blood and blood products administered between the two groups. No adverse effects of tranexamic acid were found in this study.

In conclusion, there was no significant difference in postoperative blood loss or blood and blood product requirement between those children with cyanotic CHD undergoing open heart surgery who received a single dose of tranexamic acid compared with those who received two doses.

Key word : Tranexamic Acid, Cyanotic Heart Disease, Open Heart Surgery, Postoperative Blood / Component Use

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Cardiopulmonary bypass (CPB) increases the risk of postoperative bleeding and the need for transfusion[1]. Fibrinolysis is an important cause of excessive bleeding after cardiac surgery[2,3]. Tranexamic acid (trans-4-aminomethylcyclohexane-1-carbonxylic acid) is a synthetic lysine analog that competitively binds to the lysine-binding sites of plasmin and plasminogen. It inhibits fibrinolysis with a 6-to-10-fold greater potency than aminocaproic acid[4]. Prophylactic administration of tranexamic acid reduces blood loss and transfusion requirements after cardiac surgery in adults[5-11]. Large doses of tranexamic acid effectively decrease blood loss in pediatric patients undergoing repeat cardiac surgery[12]. There is large variation (10-150 mg/kg of tranexamic acid) in the recommended dose of tranexamic acid given to reduce bleeding following cardiopulmonary bypass[13]. Therefore, we sought to compare the efficacy of a small-dose of tranexamic acid (15 mg/kg), given as a single dose or two doses in children with cyanotic heart disease, undergoing open heart operation.

MATERIAL AND METHOD

At Siriraj Hospital, between July 1999 and November 2001, 67 children with cyanotic CHD were enrolled in the study. The committee on Human Rights related to Research involving Human Subjects gave approval for the study and informed consent was obtained from their parents. Patients were enrolled in the study if they had a right-to-left shunt as a result of CHD. Preenrollment exclusion criteria consisted of age >14 yr, a history of allergy to tranexamic acid, a history of liver or renal disease, a history of coagulation disorder, or surgery involving the cavopulmonary connection.

Patients were given general anesthesia with endotracheal intubation using thiopental (2-3 mg/kg), fentanyl (10-20 μg/kg) balanced with midazolam (0.1-0.5 mg/kg), atracurium and isoflurane 0.5-1.5 per cent. A peripheral vein, a radial or femoral artery, and an internal jugular vein were catheterized. After induction of anesthesia and before skin incision, patients in both groups received tranexamic acid 15 mg/kg intravenously. At the end of CPB, the same volume of tranexamic acid (15 mg/kg) or normal saline-placebo were injected intravenously into the patients in group I and group II respectively. All solutions were prepared by an individual not involved in the study in a blind manner. Four anesthesiologists and three surgeons were involved in this study. CPB was accomplished with a Sarns HLM 9000 machine and membrane oxygenator OXIM II-34. The initial intravenous dose of porcine heparin was 3 mg/kg (300 unit/kg), with an oxygenator prime of 1-2 mg/kg to achieve a celite activated clotting time (ACT) of more than 400 seconds before the initiation of CPB. The ACT was maintained at more than 480 seconds with additional heparin as needed. After separation from bypass and atrial decannulation, the heparin was neutralized with protamine sulfate at a dose of 3.5 mg/kg. If this dose of protamine failed to return the ACT to within 10 per cent of the preheparin level, an additional dose of 0.5-1 mg/kg was given intravenously. The surgeon placed two mediastinal and pericardial tubes in all patients. These drainage tubes were connected to separate water-sealed collection reservoirs.

Total blood loss volume was defined as the total blood volume collected in the chest tube drains at 6, 12, and 24 hours, starting from the time of chest closure. This total blood loss volume specifically did not include intraoperative blood loss because it is too inaccurate for study purposes. Blood and blood components were transfused in the operating room at the direction of the attending anesthesiologist and in the ICU according to the following routine protocol for an abnormal coagulogram (PT >14 s : add protamine 0.5 mg/kg, PTT >34 s : FFP 10 ml/kg, platelet count $<10 \times 10^3/mm^3$: platelet concentrate 0.1 unit/kg). When post-operative blood loss was more than 3 ml/kg/hour and the hematocrit was less than 35 per cent, a PRC transfusion was given to raise the hematocrit to 40 per cent. The total blood transfusion volume included the total volume of whole blood, packed red cells, and blood components that were transfused during the time from the initial protamine administration until 24 hours after admission to the ICU.

Postoperative arterial blood samples were used to determine hematocrit on arrival at ICU and after that at 3, 6, 12 and 24 hours. The prothrombin time (PT), partial thromboplastin time (PTT), and platelet count were also recorded on admission to the ICU. If an abnormal coagulogram was present, the hemostatic parameters were rechecked after treatment. Any occurrence of hemodynamic instability after administration of the study drug was noted.

Thrombotic complications, postoperative renal problems, and other major morbidity and mortality were recorded.

All values are presented as mean ± standard deviation. Statistical analyses were performed using unpaired *t*-test for comparison of discrete differences between the two groups. Statistical significance for all tests was accepted as $p<0.05$.

RESULTS

Sixty-seven cyanotic children were enrolled in the study. Five patients in group II were excluded from analysis. Three of these returned to the operating room for reoperation within 12 hours due to excessive bleeding, which was clearly attributable to inadequate surgical hemostasis. The other two subjects had a pleural effusion during the first 24 hours as a result of congestive heart failure following total repair of tetralogy of Fallot. The sixty-two cases who completed the study included 33 in group I (two-dose tranexamic acid) and 29 in the group II (single dose tranexamic acid, and NSS). No patients died and no adverse effects were attributed to the administration of tranexamic acid. The patient characteristics are shown in Table 1. There was no statistical difference between the two groups with respect to age, weight, anesthetic time, surgical time, duration of CPB and aortic crossclamp time.

The preoperative and immediate ICU entry coagulation profile results for the two groups are shown in Table 2. Significant within-group reductions were seen in hematocrit and platelet count, accompanied by significant increases in ACT, PT and PTT. However, these increases of coagulation values were of equal magnitude when compared between the two groups. The reduction in hematocrit value and platelet count, which were measured on arrival in the ICU and at 24 hours postoperatively were not statistically different between the two groups. Twenty-four hours postoperation, the hematocrit were 43.8 per cent and 41.7 per cent in group I and group II respectively. Postoperative blood losses in the both treatment groups are shown in Table 3. No significant difference in total blood loss was observed between the two groups when all patients were analyzed together. Total blood and blood components transfusion volumes are shown in Table 3. In univariate analyses, the transfusion volumes of PRC, FFP and platelet were not significantly different between the two-dose tranexamic acid group and the single dose tranexamic acid group.

DISCUSSION

In this prospective, blind, placebo-controlled study, we demonstrated that patients with cyanotic CHD who were treated with two doses of

Table 1. Patient characteristics and clinical data.

Variable	Group I Two-dose tranexamic acid	Group II Tranexamic acid + NSS	P-value
Number of patients	33	29	
Age (yr)	6.81 ± 3.87	5.45 ± 3.31	0.1
Age range	1 - 14 yr	4 m - 12 yr	
Body weight (kg)	18.52 ± 8.96	16.96 ± 7.11	0.5
Anesthetic time (min)	225.33 ± 36.36	236.33 ± 50.78	0.3
Operative time (min)	194.33 ± 40.64	202.63 ± 50.17	0.5
CPB time (min)	114.16 ± 35.50	107.69 ± 35.32	0.5
Aortic crossclamp time (min)	72.25 ± 23.54	66.69 ± 32.85	0.4
Type of repair			
TOF repair	29	23	
DORV repair	1	2	
AV canal repair	1	1	
DOLV-repair MV, TV, Atrial septectomy	0	1	
TAPVC repair	1	0	
Ebstein anomaly repair	1	1	
dTGA for septectomy	0	1	

TOF = tetralogy of Fallot, DORV = double outlet right ventricle, AV canal = atrioventricular canal, DOLV = double outlet left ventricle, MV = mitral valve, TV = tricuspid valve, dTGA = transposition of great arteries, TAPVC = total anomalous pulmonary venous connection.

Table 2. Preoperative and immediate postoperative coagulation.

	Group I			Group II		
	Preop	Imm postop	24-h postop	Preop	Imm postop	24-h postop
Hematocrit (%)	54.7 ± 9.9	37.4 ± 4.9	43.8 ± 4.0	52.9 ± 9.1	36.9 ± 6.2	41.7 ± 3.7
Activated clotting time (sec)	148.7 ± 16.1	153.3 ± 15.6	-	138.9 ± 16.0	148.3 ± 14.6	-
Prothrombin time (sec)	12.3 ± 1.4	15.0 ± 1.7	-	12.7 ± 1.9	15.9 ± 2.5	-
Partial thromboplastin time (sec)	29.6 ± 4.4	36.9 ± 5.8	-	29.9 ± 3.9	37.1 ± 5.9	-
Platelet count (x 1,000/mm^3)	239.1 ± 87.1	148.4 ± 38.5	-	282.6 ± 110.4	173.2 ± 42.1	-

All within-group preoperative and immediate postoperative difference are significant ($p<0.05$).
None of between-group comparisons are significantly different.

Table 3. Postoperative blood loss and transfusion volume in Group I (two-dose tranexamic acid) and Group II (single dose tranexamic acid).

Variable		Group I	Group II	P-Value
Blood loss				
Total (ml)		195.63 ± 188.03	186.30 ± 163.78	0.5
ml/kg/24 h		12.51 ± 13.20	10.68 ± 6.38	0.5
Transfusion volume				
PRC	: Total (ml)	395.82 ± 160.50	434.04 ± 200.82	0.4
	ml/kg/24 h	23.72 ± 10.61	27.05 ± 11.28	0.2
FFP	: Total (ml)	294.22 ± 139.62	276.18 ± 152.80	0.6
	ml/kg/24 h	19.39 ± 9.98	16.21 ± 6.98	0.4
Platelet	: unit/kg/24 h	0.12 ± 0.05	0.11 ± 0.05	0.4

tranexamic acid had the same total blood loss as children who received a single dose of tranexamic acid (15 mg/kg). Additionally, the total transfusion volume requirement for PRC, FFP and platelet concentrate were of equal magnitude for each group. This finding suggests that a single dose of 15 mg/kg tranexamic acid injected as a bolus before skin incision provided the same hemostatic efficacy as an additional second bolus administrated after completion of CPB. There are a few reports of the use of tranexamic acid in cyanotic pediatric open heart surgery[12,14]. Zonis, et al. reported a reduction in postoperative blood loss and blood product requirements in cyanotic children by using a single dose of tranexamic acid at a dose of 50 mg/kg[14]. In an effort to maximize antifibrinolytic activity and the observed outcome of tranexamic acid, Reid, et al. [12] used a larger dose (100 mg/kg after induction, followed by 10 mg/kg/hour and 100 mg/kg in pump prime) in children undergoing repeat sternotomy and CPB. The results showed a reduction of 24 per cent in total blood loss in the tranexamic group when compared with the placebo group. Tranexamic acid may improve hemostasis after open heart surgery in two ways[4,15] :- 1) it blocks plasmin-induced platelet activation, consequently preserving platelet function, and 2) it is a lysine analog that effectively inhibits fibrinolysis. However, pharmacokinetic and pharmacodynamic data are limited in pediatric patients. There has been a report by Isetta, et al.[16], that showed an 80 per cent decline in the plasma concentration of tranexamic acid between the postbolus peak and the end of CPB when a continuous infusion was not used. It is possible that a single dose administered before skin incision may result in a subtherapeutic plasma concentration after CPB ends when the fibrinolytic mechanism is most significant. It may be of benefit to administer the second bolus at the termination of CPB in the pediatric population. We did not give additional tranexamic acid by continuous infusion after a bolus injection nor did we prime the patient because of concerns about a hypercoagulable state. However, thrombotic complications or other side effects are very infrequent. In adults, cases of cerebral, pulmonary, and retinal thrombosis have been reported[17-19]. No patients died and no side effects were attributed to the study drugs in either group in our study.

In conclusion, this study showed that a single dose of tranexamic acid (15 mg/kg) following induction of anesthesia and two doses of tranexamic acid (the second dose of 15 mg/kg given on completion of CPB) in cyanotic children undergoing cardiac repair had the same effect on the amount of blood loss when cardiopulmonary bypass was reversed. The amount of blood and blood product requirements were not statistically significantly different between the two groups. It is not necessary to administer an additional dose of tranexamic acid at the termination of cardiopulmonary bypass. Tranexamic acid was well tolerated by all patients in this study. There were no hemodynamic instability, thrombotic complications, or other adverse reactions associated with the drugs.

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การใช้ยา tranexamic acid ลดการให้เลือดและส่วนประกอบของเลือดในการผ่าตัดหัวใจผู้ป่วยเด็กโรคหัวใจพิการแต่กำเนิดชนิดเขียว

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ผู้ป่วยเด็กโรคหัวใจพิการแต่กำเนิดที่มารับการผ่าตัดแก้ไขความพิการของหัวใจภายใต้การใช้เทคนิคหัวใจ-ปอดเทียม มีปัญหาของเลือดออกมากหลังผ่าตัดจากความผิดปกติของเลือดแข็งเป็นลิ่ม ทำให้จำเป็นต้องให้เลือดและส่วนประกอบของเลือด รักษาให้มีลิ่มเลือดเพียงพอที่จะหยุดเลือดออก ได้มีการใช้ยา tranexamic acid (transamin) ซึ่งออกฤทธิ์ขัดขวางขบวนการ fibrinolysis เพื่อลดการเสียเลือดในการผ่าตัดหัวใจผู้ป่วยแพร่หลาย โดยใช้ขนาดตั้งแต่ 10–150 มก/กก บริหารเข้าหลอด-เลือดดำแบบครั้งเดียว หรือหยดเข้าหลอดเลือดและใส่ในเครื่องหัวใจ-ปอดเทียม แต่มีการใช้ยานี้ในเด็กน้อยมาก โดยเฉพาะกลุ่มหัวใจพิการชนิดที่มีเลือดลัดทางจากขวาไปซ้าย ดังนั้นคณะผู้ศึกษาจึงได้นำยานี้มาใช้เพื่อหวังผลลดการเสียเลือด และลดการให้เลือดและส่วนประกอบของเลือดในผู้ป่วยเด็กหัวใจพิการแต่กำเนิดชนิดเขียวที่มารับการผ่าตัดแก้ไขความพิการของหัวใจภายใต้เทคนิคใช้หัวใจ-ปอดเทียม ทำการศึกษาในผู้ป่วยกลุ่มนี้ 67 ราย อายุ 4 เดือน - 14 ปี, น้ำหนัก 6–27 กก โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่ม 1 (33 ราย) ได้รับ transamin 2 ครั้ง ขนาด 15 มก/กก ครั้งแรกก่อนลงมีดผ่าตัดและครั้งที่ 2 หลังหยุดใช้เครื่องหัวใจ-ปอดเทียม กลุ่มที่ 2 (34 ราย) ได้รับ transamin 15 มก/กก ครั้งเดียวบริหารเข้าหลอดเลือดดำก่อนลงมีดผ่าตัด, ทำการบันทึกค่า ฮีโมโตคริต และ coagulation (ACT, PT, PTT, ปริมาณเกล็ดเลือด) ก่อนผ่าตัด และหลังผ่าตัด บันทึกปริมาณเลือดออกหลังผ่าตัด 24 ชั่วโมง และบันทึกปริมาณของเลือด และส่วนประกอบของเลือดที่ให้แก่ผู้ป่วย ผลที่ได้จากการศึกษา ผู้ป่วยทั้ง 2 กลุ่ม มีคุณลักษณะทางคลินิกไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ มีการคัดผู้ป่วย 5 รายออกจากกลุ่มที่ 2 เนื่องจากต้องรับการผ่าตัดซ้ำเนื่องจากหยุดเลือดออกไม่ดี 3 ราย และผู้ป่วยอีก 2 ราย มี pleural effusion จากภาวะหัวใจล้มเหลว พบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติของผู้ป่วยทั้ง 2 กลุ่ม ในเรื่องของปริมาณเลือดออกหลังผ่าตัดหัวใจ รวมทั้งปริมาณของเลือดและส่วนประกอบของเลือดที่ให้แก่ผู้ป่วย ไม่พบภาวะแทรกซ้อนของระบบไหลเวียนเลือดและไม่พบผลที่ไม่พึงประสงค์อื่น ๆ ที่เกิดจาก transamin ซึ่งสรุปได้ว่า การให้ยา transamin 15 มก/กก หนึ่งหรือสองครั้งก็ไม่มีความแตกต่างกันในเรื่องของปริมาณเลือดออกหลังผ่าตัด รวมทั้งปริมาณเลือดและส่วนประกอบของเลือดที่ให้แก่ผู้ป่วยเด็กหัวใจพิการแต่กำเนิดชนิดเขียวที่มารับการผ่าตัดแก้ไขความพิการด้วยเทคนิคใช้เครื่องหัวใจ-ปอดเทียม

คำสำคัญ : กรดทรานเอกซามิก, โรคหัวใจพิการแต่กำเนิดชนิดเลือดลัดทางจากขวาไปซ้าย, การผ่าตัดหัวใจ, การใช้เลือด/ส่วนประกอบ หลังผ่าตัด

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