Pediatric Anesthesia 2005 **15**: 41–46 doi:10.1111/j.1460-9592.2004.01366.x

Which may be effective to reduce blood loss after cardiac operations in cyanotic children: tranexamic acid, aprotinin or a combination?

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Summary

Background: Children with cyanotic heart disease undergoing cardiac surgery in which cardiopulmonary bypass is used are at increased risk of postoperative bleeding. In this study, the authors investigated the possibility of reducing postoperative blood loss by using aprotinin and tranexamic acid alone or a combination of these two agents.

Methods: In a prospective, randomized, blind study, 100 children undergoing cardiac surgery were investigated. In group 1 ($n = 25$) patients acted as the control and did not receive either study drugs. In group 2 ($n = 25$) patients received aprotinin (30.000 KIU·kg^{-1} after induction of anesthesia, 30.000 KIU·kg^{-1} in the pump prime and 30.000 KIU·kg^{-1} after weaning from bypass). In group 3 ($n = 25$) patients received tranexamic acid (100 mg·kg^{-1} after induction of anesthesia, 100 mg·kg^{-1} in the pump prime and 100 mg·kg^{-1} after weaning from bypass). In group 4 ($n = 25$) patients received a combination of the two agents in the same manner. Total blood loss and transfusion requirements during the period from protamine administration until 24 h after admission to the intensive care unit were recorded. In addition, hemoglobin, platelet counts and coagulation studies were recorded.

Results: Postoperative blood loss was significantly higher in the control group (group 1) compared with children in other groups who were treated with aprotinin, tranexamic acid or a combination of the two agents (groups 2, 3 and 4) during the first 24 h after admission to cardiac intensive care unit (40 ± 18 ml·kg^{-1}·24 h^{-1}, aprotinin; 35 ± 16 ml·kg^{-1}·24 h^{-1}, tranexamic acid; 34 ± 19 ml·kg^{-1}·24 h^{-1}, combination; 35 ± 15 ml·kg^{-1}·24 h^{-1}). The total transfusion requirements were also significantly less in the all treatment groups. Time taken for sternal closure was longer in the control group (68 ± 11 min) compared with treatment groups 2, 3 and 4, respectively (40 ± 18, 42 ± 11,

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42 ± 13 min, $P < 0.05$). The coagulation parameters were not found to be significantly different between the three groups.
Conclusions: Our results suggested that both agents were effective to reduce postoperative blood loss and transfusion requirements in patients with cyanotic congenital heart disease. However, the combination of aprotinin and tranexamic acid did not seem more effective than either of the two drugs alone.

Keywords: cyanosis; children; aprotinin; tranexamic acid; heart disease

Introduction

Postoperative bleeding is a common complication after cardiac operations with cardiopulmonary bypass (CPB) and is even more important in children with cyanotic heart disease (1, 2). It is related to preexisting coagulation anomalies, platelet dysfunction and abnormal fibrinolysis (3), unwanted effects of CPB such as dilution of coagulation factors and exposure of the blood to the artificial surfaces of the extracorporeal circuit (4). Despite the prophylactic use of antifibrinolytic agents such as aprotinin and tranexamic acid to reduce blood loss in pediatric cardiac surgery, neither an accepted dosing regimen nor the effectiveness of these drugs has been well established to date.

The hypothesis of the present study was to investigate the effects of aprotinin and tranexamic acid alone or their combination on postoperative bleeding in cyanotic patients undergoing cardiac surgery using CPB.

Materials and methods

After institutional approval by the Ethics Committee and informed parental consent, 100 children with cyanotic congenital heart disease undergoing a variety of corrective cardiac procedures with CPB were examined in a prospective, blinded and randomized study. Patients for repeated surgery for example, children who had undergone a previous shunt procedure throughout a lateral thoracotomy, without exposure to antifibrinolytic agents were included. Patients undergoing reoperations with sternotomy within 6 months after using aprotinin or tranexamic acid and patients that required emergency operations were excluded. Also patients taking aspirin, dipyridamole or other anticoagulants and known coagulation disorders, known metabolic disorders, renal or hepatic insufficiency, or previous exposure to aprotinin or tranexamic acid were not included the study.

The children were randomly allocated into four groups and this was known by the anesthesiologist and perfusionist. The surgeon was unaware of the group allocation. All blood loss throughout the procedure was recorded by trained nursing personnel who were unaware of each patient's group allocation. Postoperative care was directed by a separate team of two cardiac surgeons and one pediatric cardiologist, also blinded to the antifibrinolytic drug given during the operation. Group 1 ($n = 25$) acted as the control group and received none of the study drugs. Group 2 ($n = 25$) received 30.000 KIU·kg^{-1} aprotinin after anesthetic induction, 30.000 KIU·kg^{-1} in the CPB prime and 30.000 KIU·kg^{-1} after weaning from CPB until skin closure. Group 3 ($n = 25$) received 100 mg·kg^{-1} tranexamic acid after anesthetic induction, 100 mg·kg^{-1} tranexamic acid in the CPB prime and 100 mg·kg^{-1} after weaning from CPB until skin closure. Group 4 ($n = 25$) received a combination of both aprotinin and tranexamic acid in the same protocol.

All children were premedicated orally with midazolam 0.5 mg·kg^{-1} 45 min before operation. Anesthesia was induced with fentanyl 20 μg·kg^{-1}, rocuronium 0.6 mg·kg^{-1}, midazolam 0.1 mg·kg^{-1} to facilitate tracheal intubation. Maintenance of anesthesia was with remifentanil (0.05–0.2 μg·kg^{-1}·min^{-1}) and sevoflurane 1–1.5% with air and oxygen (50%). After inititation of CPB and after weaning; additional doses of rocuronium 0.2 mg·kg^{-1} and midazolam 0.1 mg·kg^{-1} were given. Volume ventilation was adjusted to maintain $PaCO_2$ between 4 and 4.6 kPa (30–35 mmHg). In all patients, a median sternotomy was

performed. Heparin 300 $U \cdot kg^{-1}$ was administered before commencing CPB, and additional doses were given as needed to keep the activated clotting time above 450 s. The CPB circuit consisted of a nonpulsatile roller pump (Stöckert-Shiley, model 10.10.000, Munich, Germany) and a membrane oxygenator (Minimax Plus, Medtronic Inc., Anaheim, CA, USA). The priming solution consisted of isotonic sodium chloride supplemented with 3.000 U of heparin, 3 $ml \cdot kg^{-1}$ mannitol, 30 $mg \cdot kg^{-1}$ methyl prednisolone, 30 mmol sodium bicarbonate and fresh whole blood was added to the prime to achieve a hematocrit of 25% during CPB. Pump flows were 2.4–2.6 $l \cdot min^{-1} \cdot m^2$ during the normothermic period and decreased to 2.0 $l \cdot min^{-1} \cdot m^{-2}$ during cooling. Cold blood cardioplegia with 25 $mmol \cdot l^{-1}$ of potassium (30 $ml \cdot kg^{-1}$ for induction) was injected into the aortic root and repeated every 20 min. Acid–base status and blood gases were adjusted according to the alpha-stat method during CPB. Moderate hypothermia (26°C–28°C) was used during CPB. For vasodilation in cooling and rewarming periods, all children received phentolamine (0.1 $mg \cdot kg^{-1}$). Conventional ultrafiltration was begun during rewarming until weaning from CPB. After separation from bypass, neutralization of heparin was achieved with protamine sulfate in a 1 : 1.5 ratio. Dopamine infusions were kept to a rate <10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the occasional patient who required additional inotropic support received an epinephrine infusion in a dose 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. All operations were performed by the same anesthesiologist and pediatric cardiac surgeon, to rule out variation in surgical technique as a cause of varying postoperative blood loss.

The closure time was defined as the interval from aortic decannulation to sternal closure minus any interval of hemodynamic instability.

Total blood loss volume was defined as the total blood volume collected in the surgical suction and in the chest tubes minus irrigation fluid during the time period extending from the initial protamine administration until 24 h after admission to the cardiac intensive care unit (CICU).

Total blood transfusion volume included the volume of all whole blood and packed red cells that were transfused during the time from the initial protamine administration until 24 h after admission to the CICU. The intraoperative post-CPB transfusion policy was to administer whole fresh blood at a hemotocrit of less than 30%. Platelets and fresh frozen plasma were administered empirically when the surgeon judged that there was excessive bleeding in the surgical field. The transfusion protocol in CICU was similar to the intraoperative policy. Fresh frozen plasma was administered when the prothrombin time was greater than 25 s or for excessive bleeding. Excessive bleeding was defined as drainage from the chest tubes more than 4 $ml \cdot kg^{-1} \cdot h^{-1}$ during any hour. Postoperative management was directed by the two cardiac surgeons and pediatric cardiologist, blinded to the study drug given during the operation.

Arterial blood samples were taken after anesthesia induction and 24 h postoperatively. Hemoglobin concentration, platelet count and coagulation studies were measured by routine laboratory methods. In addition, routine laboratory examination including serum electrolytes, and renal and liver values was performed.

Cases of thrombotic complications, postoperative renal dysfunction, and other major morbidity and mortality were recorded.

Normally distributed data were analyzed by analysis of variance (ANOVA) and expressed as mean and SD. The Student's and Neuman–Keuls Multiple Comparison test were used to determine intergroup significance. The level of statistical significance was assumed as $P < 0.05$.

Results

The study was planned with 100 children with cyanotic congenital heart disease undergoing corrective cardiac procedures. One patient in the control group, died on the operating table with deteriorating cardiac function and was withdrawn from the study. Another patient in the aprotinin group was removed from the analysis because full data were not completed and 98 children completed the study. Operative procedures of the patients entered in the study were similarly ditributed in the groups and are shown in Table 1.

Patient characteristics and intraoperative variables are shown in Table 2. Time taken for sternal closure was longest in group 1 (68 ± 11 min) and significantly different than the treatment groups (group 2; 40 ± 18 min, group 3; 42 ± 11 min and group 4; 42 ± 13 min).

Table 1
Operative procedures performed

Operations	*Group 1* (n = 24)	*Group 2* (n = 24)	*Group 3* (n = 25)	*Group 4* (n = 25)
TOF repair	12	11	15	13
TAPVR repair	8	6	2	5
BDG	3	5	7	5
TGA	2	3	1	2

TOF, tetralogy of Fallot; TAPVR, total anomalous venous return; BDG, bidirectional Glenn; TGA, transposition of great arteries.

Postoperative blood loss and transfusion requirements during the first 24 h after admission to CICU are summarized in Table 3. The control group (group 1) had a significant difference in postoperative blood loss at 24 h (40 ± 18 ml·kg^{-1}·24 h^{-1}) compared with the treatment groups, respectively (group 2; 35 ± 16 ml·kg^{-1}·24 h^{-1}, group 3; 34 ± 19 ml·kg^{-1}·24 h^{-1} and group 4; 35 ± 15 ml·kg^{-1}·24 h^{-1}, $P < 0.05$). Also total transfusion requirements during the first 24 h were less in the treatment groups compared with the control group. Packed red cell blood use was greatest in group 1; 25 ± 15 ml·kg^{-1}·24 h^{-1}, in group 2; 18 ± 12 ml·kg^{-1}·24 h^{-1}, in group 3; 16 ± 14 ml·kg^{-1}·24 h^{-1}, and in group 4; 14 ± 12 ml·kg^{-1}·24 h^{-1}. When treatment groups were compared, no statistical difference was found for postoperative blood loss and transfusion requirement between the group 2, 3 and 4 (Tables 4 and 5). Additionally, there were no statistical differences between groups in any of the coagulation parameters. No apparent drug-related adverse events were observed.

Table 3
Blood loss and transfusion requirements during the first 24 h postoperatively (ml^{-1}·kg^{-1}·24 h^{-1})[a]

	Group 1 (n = 24)	*Group 2* (n = 24)	*Group 3* (n = 25)	*Group 4* (n = 25)	P-*value*
Blood loss (ml·kg^{-1}·24 h^{-1})	40 ± 18	35 ± 16	34 ± 19	35 ± 15	<0.05[b]
PRBC (ml·kg^{-1}·24 h^{-1})	25 ± 15	18 ± 12	16 ± 14	14 ± 13	<0.05[b]
FFP (ml·kg^{-1}·24 h^{-1})	21 ± 14	14 ± 11	13 ± 12	10 ± 10	<0.05[b]

[a]Values are in ml·kg^{-1}·24 h^{-1} and expressed as mean ± SD.
[b]$P < 0.05$ group 1 versus groups 2–4.
PRBC, packed red cell blood; FFP, fresh frozen plasma.

Discussion

Increased risk of bleeding in children with congenital heart diseases particularly infants with cyanotic heart disease is a serious problem. These patients are known to have a preexisting deranged coagulation system (5). In addition, use of CPB during cardiac surgery causes a severe impairment of the coagulation system by initiating fibrinolysis and causing platelet dysfunction (6). Especially for children who are undergoing surgery for complex cardiac procedures; time from protamine administration to skin closure after CPB is extremely important in morbidity and mortality. It has been shown that increasing surgical operating time is associated with a postoperative decline of ventricular function (7).

Prophylactic use of various antifibrinolyic agents such as aprotinin or tranexamic acid to reduce blood loss from CPB-induced fibrinolysis has been popular for several years in adult cardiac surgery. The use or the dosage regimen of these antifibrinolytic agents in the pediatric age group still remains controversial.

Aprotinin, a serin protease inhibitor, has been shown to decrease postoperative bleeding and transfusion requirements in adult patients undergoing cardiac operations with CPB (8, 9). The hemostatic effect of aprotinin is ascribed to its antifibrinolytic

Table 2
Patient characteristics and intraoperative variables[a]

	Group 1 (n = 24)	*Group 2* (n = 24)	*Group 3* (n = 25)	*Group 4* (n = 25)
Age (year)	2.3 mo to 8 y	2 mo to 5 y	3.2 mo to 9.7 y	2.5 mo to 8.1 y
Age (year)	3.8 ± 2.4	3.1 ± 2.8	4.1 ± 2.0	3.6 ± 2.5
M/F	12/13	11/14	15/10	13/12
Weight (kg)	5.8 ± 2.4	5.1 ± 2.4	6.2 ± 3.1	5.9 ± 2.6
CPB time (min)	106 ± 23	119 ± 12	105 ± 10	113 ± 12
Cross-clamping (min)	76 ± 13	77 ± 12	78 ± 14	77 ± 14
Temperature (°C)	28.2 ± 0.5	26.5 ± 1.3	28. 2 ± 1.2	27.1 ± 0.6
Total heparin (IU·kg^{-1})	425 ± 35	405 ± 25	459 ± 12	475 ± 20
Urine on CPB (ml·kg^{-1}·h^{-1})	3.5	4.1	3.8	3.6
Sternal closure time (min)	68 ± 11	40 ± 18	42 ± 11	42 ± 13

[a]Values are mean ± SD; CPB, cardiopulmonary bypass.

Table 4
Hematological values and coagulation tests at 24 h[a]

	Group 1 (n = *24*)	*Group 2* (n = *24*)	*Group 3* (n = *25*)	*Group 4* (n = *25*)	P < *0.05*
Hemoglobin ($gm \cdot dl^{-1}$)	14.3 ± 1 2	13.2 ± 1.3	14.1 ± 2.0	14.1 ± 1.1	NS
ACT (s)	125 ± 11	123 ± 10	120 ± 11	120 ± 10	NS
Platelets ($10^9 \cdot l^{-1}$)	155 ± 23	161 ± 24	156 ± 22	154 ± 23	NS
PT (s)	14 ± 4	15 ± 3	15 ± 3	14 ± 4	NS
PTT (s)	68 ± 10	67 ± 9	68 ± 11	67 ± 9	NS
Fibrinogen ($mg \cdot dl^{-1}$)	209 ± 11	219 ± 11	212 ± 12	215 ± 11	<0.05[b]

[a]Values are mean ± SD.
[b]Group 1 versus group 2–4.
ACT, activated clotting time; PT, protrombin time; PTT, partial thromboplastin time; NS, not significant.

Table 5
Blood values at 24 h[a]

	Group 1 (n = *24*)	*Group 2* (n = *24*)	*Group 3* (n = *25*)	*Group 4* (n = *25*)	P < *0.05*
Creatinine ($\mu mol \cdot l^{-1}$)	54 ± 1 2	49 ± 1.3	56 ± 2.0	55 ± 1.1	NS
Blood urea ($mmol \cdot l^{-1}$)	4.5 ± 1.1	4.3 ± 1.0	4.7 ± 1.1	4.4 ± 1.2	NS
AST ($U \cdot l^{-1}$)	38 ± 13	36 ± 14	36 ± 12	34 ± 13	NS
ALT ($U \cdot l^{-1}$)	40 ± 14	38 ± 13	35 ± 13	41 ± 11	NS
LDH ($U \cdot l^{-1}$)	430 ± 60	457 ± 49	398 ± 51	417 ± 63	NS

[a]Values are mean ± SD; NS, not significant.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

properties and preserving effect on platelet function (10, 11). Despite its widespread use in adult cardiac surgery, a consensus has not been reached concerning patient selection and dosage in pediatric cardiac surgery. A small blood volume connected to a relatively high-volume extracorporeal circuit makes the calculation of a dosage regimen more complicated. Previous studies with the use of aprotinin in pediatric patients reported conflicting results. Davies *et al* studied 42 patients designed to receive placebo or aprotinin and found aprotinin to be of no benefit in routine cardiac operations (12). Boldt *et al*. found less than 35.000 $KIU \cdot kg^{-1}$ aprotinin did not reduce postoperative blood loss (13). In another study, no beneficial effect of aprotinin on blood loss could be demonstrated in patients with ventricular septal defect (VSD) or tetralogy of Fallot (TOF), in terms of blood loss and transfusion requirements, but only in patients with complex cardiac pathology such as transposition of great arteries (TGA) (14). In a new study, it was shown that aprotinin reduced operative closure time and blood use in pediatric patients undergoing CPB who were 6 months of age or less or who underwent reoperation (15).

One of the other antifibrinolytic agents widely used in adult cardiac surgery is tranexamic acid. It is shown that tranexamic acid has a reversible inhibition of absorption by lysine analogs, displaces plasminogen and effectively inhibits fibrinolysis and is roughly ten times more potent on a molar basis and has a longer half-life, a higher and more sustained antifibrinolytic activity in tissue than epsilon–aminocaproic acid (16). However, its efficacy has not been extensively studied in pediatric cardiac patients. In a double-blind study, there was no significant difference in postoperative blood loss in acyanotic children undergoing open heart surgery who received either a placebo dose or a single dose of tranexamic acid. However, when the children with cyanosis were analyzed separately, there was a highly significant difference in blood loss between the groups (17). Isetta *et al.* reported that in children, tranexamic acid plasma concentration between the postbolus peak and the end of CPB has an 80% decline when a continuous infusion was not used (18). In some other studies, it is reported that a large dose of tranexamic acid effectively reduces blood loss in children undergoing cardiac reoperation (19, 20).

In our study, both agents in high doses seemed to be effective compared with a control group in reducing blood loss in cyanotic children undergoing primary cardiac surgery. However, the combination of these two agents was not more effective than either of the

two agents alone. In a similar study, Chauhan *et al*. studied 100 children with congenital heart disease who received placebo, aprotinin, epsilon aminocaproic acid (EACA) or a combination (21). They suggested that the action of combination of EACA and aprotinin were complementary because EACA acts by inhibiting plasminogen activator substances, and to a lesser degree by antiplasmin activator and aprotinin acts by inhibiting plasmin and kallikrein and other proteases. But even with this, the results of their combination therapy were not statistically more effective than either of the two agents.

Because of conflicting results reported in the literature, it is still impossible to define recommendations regarding the efficacy and the optimal dosage of aprotinin and tranexamic acid in pediatric cardiac surgery, even when the study was double-blinded and randomized. The majority of studies investigating efficacy have included a highly heterogeneous population of cardiac malformations. In the present study, both agents in the doses we used seem to be effective to reduce blood loss after cardiac operations in cyanotic children. A combined use of aprotinin and tranexamine was not more effective than using either aprotinin or tranexamine alone to reduce postoperative blood loss. However, the absence of a dose–response protocol limited the conclusions that could be made regarding the efficacy of combination therapy.

In conclusion, our study has demonstrated no benefit in the routine use of a combination therapy in cyanotic children undergoing cardiac surgery. However, larger groups of studies may be required to examine the effects of combination of these antifibrinolytic agents and dose–response studies and detailed studies of coagulation may be necessary to examine the combination effect of these drugs in cyanotic children undergoing cardiac surgery.

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Accepted 15 February 2004