Effect of Tranexamic Acid after Cardiac Surgery in Children

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Abstract:

Background: *The antifibrinolytic drug tranexamic acid (TA) decreases blood loss in Pediatric patients under going cardiac Surgery. However its efficacy has not been extensively studied in children.*

Method: *We examined 750 children under going cardiac surgery form 2004 to 2007 in National Institute of Cardiovascular Diseases (NICVD), 379 children in the Tranexamic Acid group (TA) and 371 included in placebo (P) group. After induction of anesthesia and prior to skin incision, patients received either tranexamic acid (10mg/kg followed by 1mg/kg/hr) and saline placebo. After admission to intensive care unit total blood loss and transfusion requirements during the first12 hours were recorded.*

Result: *Children who were treated with tranexamic acid had 24% less total blood loss (26±7 vs 34±17 ml/kg) compared with children who received placebo ($p<0.05$). Additionally, the total transfusion requirements, total donor unit exposure and financial cost of blood components were less in the tranexamic acid group.*

Conclusion: *Tranexamic acid can reduce perioperative blood loss in children undergoing cardiac surgery.*

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Introduction:

Tranexamic acid can reduce perioperative blood loss in children undergoing cardiac surgery.

Bleeding remains a significant complication of open-heart surgery. In congenital heart disease of children there is increased risk of postoperative bleeding.[1] Post cardiopulmonary bypass platelet dysfunction, dilutional coagulopathy and abnormal fibrinolysis contribute to this bleeding tendency.[1] We are here discussing the haemostatic effect of tranexamic acid, a potent antifirbinolytic agent in an effect to determine whether the salutary effect of Tranexamic acid. Tranexamic acid is a lysine analog that competitively binds to the lysine binding sites of plasmin and plasminogen. It inhibits fibrinolysis with 6 to 10 fold greater potency than any other antifibrinolytic drugs. TA effectively reduces blood loss and transfusion requirements after cardiac surgery in children.[2] We evaluate the efficacy of TA utilizing a loading dose (10 mg/kg after induction, followed by 1 mg/kg/hr) in a population of children.

Methods:

We reviewed 750 consecutive paediatric congenital cardiac surgical patients from 2004 to 2007. Frequency and volume of blood product transfusion, postoperative blood loss, cardio pulmonary bypass (CPB) time, procedure and demographics are collected.

Total red cells unit exposure (whole blood units and packed red cell units) and total non red cell unit exposure (platelet units, cryoprecipitate units and fresh frozen plasma units) included the respective units that were transfused during the time period extending from entry into the operating room until 12 hours after admission in the ICU.

Total donor exposure was defined as the sum of total red cell unit exposure and total non red cell unit exposure. 'Closure time' was defined as the

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interval from aortic decannulation to sternal closure minus any interval of hemodynamic instability.

Group Assignment:
A table of random numbers determined patient's allocation to one of the two groups. The placebo group (group p) received saline infusions. A second group (group TA) received tranexamic acid beginning after induction of anesthesia but before skin incision (loading dose 10 mg.kgÎ¹ for 30 minutes) followed by a 12-hour infusion of 1 mg.kgÎ¹.hr Î¹.

Anticoagulation:
Heparin (400 units kg^{-1}) provided anticoagulation for ECC (extracorporeal circulation) and noted activated coagulation time greater than 450 seconds, determines in duplicate every 30 minutes, ensured continued anticoagulation. For ECC, nonocclusive roller pumps, membrane oxygenators, cold blood cardioplegic arrest and systemic hypothermia to 28^0C were used. The ECC circuit initially contained 5,000 units of heparin in 500 ml clear fluid prime. Termination of ECC required a rectal temperature of 37^0C. After ECC, protamine (1.5 mg kg^{-1}) used to neutralize heparin to obtain an activated coagulation time within 15 seconds of baseline.

Transfusion:
All red cells transfused in the first 12 hours were weighted before administration. The weight of the filled container minus that of an empty bag (34 gm) constituted the mass administered. After 12 hours strict transfusion criteria no longer applied.[3]

Blood Loss:
The mass of blood collected via mediastinal drains over 12 hours constituted blood loss. No attempt was made to estimate blood loss before or during ECC or before insertion of mediastinal drainage tubes. We ignored estimates of irrigation fluid, sponged suction container losses and soaking of lines. All these minor components of operative blood loss are notoriously inaccurate.

Coagulation tests:
Before induction of anesthesia and again 2 hours after completion of initial protamine infusion, assessment of coagulation proceeded.

Data analysis:
Paired student t test compared postoperative versus preoperative coagulation data. Frequency data underwent contingency table analysis using likelihood ratio × statistics. All tests are two tailed, with $p < 0.05$ denoting significance.

Results:
The 750 subjects who completed the study included 379 in the tranexamic acid group and 371 is the placebo group. Independent variables are shown in Table I. There was no statistical difference between the two groups with respect to age, weight, height, preoperative hematocrit, platelet count and arterial oxygen saturation. Medium duration of cardiopulmonary bypass was 18 minutes greater in the placebo group (112 ± 19 vs 94 ± 21 min, $p= 0.01$). The aortic cross clamp time, nadir oesophageal temperature and total heparin administration prior to and during bypass were comparable between the groups. Fresh whole blood (defined as less than 4 days old) was available 48 % of the time in placebo group and 25 % of the time in tranexamic acid group ($p= 0.03$).

TA was well tolerated by all subjects in the treatment group. There were no cases of haemodynamic instability, overt thrombotic complication or other adverse effects associated with the bolus of infusion.

Dependent variables are summarized in table 2. In univariate analysis total blood loss was reduced by 24%. ($p = 0.03$) and total blood transfusion volume was reduced by 38% ($p = 0.04$) in the group that received TA.

The total red blood cell exposure was 2.0 units in the TA group versus 3.0 units in the placebo group ($p = 0.06$) and the total donor exposure was 3.0 versus 4.0 units respectively ($p = 0.10$). The time interval from aortic decanulation to sternal closure (Closure time) was 32% shorter in the TA group (15 ± 6 vs 22 ± 6 min, $p = 0.01$). Subjects in the TA group also tended to have a 30 min shorter total operating room time (3.8 ± 1.0, 4.0 ± 1, $p = 0.15$). The duration of mechanical ventilation in the ICU (19 ± 2 vs 17 ± 9 hr, $p = 0.90$) and the total time spent in the ICU (48 ± 14 vs 51 ± 13 hr, $p = 0.07$) was not significantly different between tranexamic acid and placebo group. The hematocrit value, which was measured upon arrival in the ICU, was demonstrated to be statistically different between two groups (40 ± 4 % in TA group vs $33 \pm$ in the placebo group, $p = 0.01$).

Table I

Independent variables:

Variables	Placebo	TA
Sample	n=371	n=379
Age	6.1 ± 1.8	6.2 ± 2.2
Weight(kg)	12.5 ± 5.7	12.5 ± 5.1
Height(cm)	90 ± 33	79 ± 18
Preoperative haematocrit value	40 ± 5	43 ± 5
Preoperative platelet count	261 ± 60	311 ± 59
Preoperative Spo2 (%)	89 ± 11	88 ± 7
Cyanotic (Spo2< 90%)	192/371(52%)	189/379(50%)
Extracorporeal bypass time (min)	112 ± 19	94 ±21
Aortic cross clamp time (min)	53 ± 37	37 ± 28
Total heparin value (u/kg)	440 ± 56	470 ± 84
Nadir oesophageal temperature(°C)	24.7 ± 2	25.7 ± 3.8
Fresh whole blood available	178/371 (48%)	94/379 (25%)

Table-II

Transfusion outcome measures:

	Total blood loss (ml/kg)		Total RBC transfusion volume (ml/kg)		Total donor exposure (unit)		Total red cell exposure (unit)	
	P=0.03		*P=0.04*		*P=*		*P=0.06*	
Measure	P	TA	P	TA	P	TA	P	TA
Value	34±17	26±7	39±20	24 ± 5	4.0±32	3.0±1.4	3.0±0.5	2.0±0.4

(P= placebo, TA= Tranexemic acid, *p*= pvalue)

Discussion:

In this prospective, placebo-controlled study, we demonstrated that children who were treated with large dose tranexamic acid had 24 % less total blood loss compared with children who received placebo. Additionally, the total volume transfusion requirements and total unit exposure to banked blood components were less in the tranexamic acid group.

In this study no thrombotic events or other adverse effect were detected. Our findings are parallel to those of similar trials in adult cardiac surgical population.[3]

We conclude that in paediatric patients undergoing cardiac surgery tranexamic acid effectively reduces blood loss.

There has been much variation in the tranexamic acid dosing regimen.[1] Complications attributed to tranexamic acid in the adult patients are very infrequent. The most critical concern is that tranexamic acid may promote a hypercoaguable state. Cases of cerebral, pulmonary, mesenteric and retinal thrombosis have been reported.[1]

Normal coagulation does not return until approximately 12 hours after surgery at which time TA plasma levels have declined (plasma half life approximately 80 minutes). TA costs considerably less than any other antifibrinolytic agent (like aprotinin). Furthermore, aprotinin use complicates monitoring anticoagulation therapy during surgery with the activated coagulation time whereas TA does not interfere with this simple, inexpensive, widely used technique.[3]

The association between aprotinin and serious end-organ damage (renal, cardiac or cerebral) indicates that continued use is not prudent. In contrast, the less expensive generic medications aminocaproic acid (ACA) and TA are safe alternatives.[6]

ACA / TA have also been found to be beneficial in neonates requiring surgery while on Extra Corporeal Membrane Oxygenator (ECMO)[5]. The

prophylactic use of TA to decrease blood loss after CPB was first reported in 1988.[4]

Harrow and colleagues[5] conducted a dose-response study in 148 cardiac surgical patients. The initial loading doses in this trial were 0.25, 5, 10, 20 and 40 mg/kg, followed by an infusion of one-tenth the bolus per hour. These investigators found that 10 mg/kg decreased bleeding 34% compared with placebo.[1]

Conclusion:

The antifibrinolytic drug tranexamic acid (TA) decreases blood loss in paediatric patients undergoing cardiac surgery. Children who were treated with tranexamic acid had 24% less total blood loss. Additionally, the total transfusion requirements, total donor unit exposure and financial cost of blood components are less in the tranexamic acid group. Prophylactic tranexamic acid can reduce perioperative blood loss in children undergoing cardiac surgery.

Conflict of Interest - None.

References:

1. Reid RW, Zimmerman A, Laussen PC. The Efficacy of Tranexamic Acid versus Placebo in Decreasing Blood Loss in Pediatric Patients Undergoing Repeat Cardiac Surgery. *Anesthesia Analgesia* 1997; 84: 990-6.
2. Zaris Z, Secar M, Reichard C et al. The effect of preoperative tranexamic acid on blood loss after cardiac operations in children. *Journal Thoracic Cardiovascular Surgery* 1996; 111: 982-7
3. Harrow JC, Daniel F, Riper V. Hemostatic effect of Tranexamic acid and Desmopressin During Cardiac Surgery. *Circulation* 1991; 84: 2063-2070
4. Francuis J, Desrochos J. Natural and synthetic antifibrinolytics in Cardiac Surgery. *Canadian Journal of Anesthesia* 1992; 39: 353-365.
5. Harrow J, Havacek J, String MD et al. Prophylactic Tranexamic Acid decreases bleeding after cardiac operation. *Journal of thoracic and Cardiovascular Surgery* 1990; 99: 70-74.
6. Buck ML. Use of aminocaproic acid in children undergoing Cardiac Surgery and ECMO. *Paediatric Pharmacotherapy* 2006; 12: 1-4.
7. Mangano DT, Tadorya IC. The risk Associated with aprotinine in cardiac surgery. *N Eng J Med.* 2006; 354: 353-365.