

Efficacy of High Dose Tranexamic Acid in Decreasing Bleeding after Cardiac Surgery for Cyanotic Congenital Heart Disease in Children Less than Ten Kilo Body Weight

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Abstract

Background: To determine the effect of high dose tranexamic acid in decreasing immediate postoperative bleeding in children less than ten kilo body weight after complex cardiac surgery and also to evaluate the safety of high dose in small children. **Methods:** Between January-December 2015, 25 children weighing less than ten kilogram body weight underwent complex cardiac surgery for cyanotic congenital heart disease. All children were given dose of 100 mg/kg tranexamic acid at the time of anaesthetic induction and also 100 mg/kg into the CPB prime. The Median age and weight was 80 days (3 - 365) and 4.69 kg (2.4 - 7.8) respectively. The Median preoperative Hb was 10 g/dl (9.6 - 19.5 g/dl). Cardiac surgery included total intracardiac repair for TOF in 10 pts (40%), TAPVC repair in 6 (24%), arterial switch operation in 6 pts (24%), BD glenn in 1, repair of DORV with VSD in 1 and VSD closure with scimitar vein reimplantation in 1 pt. Median CPB time was 127 minutes (97 - 343) and cross clamp time was 99 (67 - 200) minutes. Moderate to deep hypothermia was maintained in all with median temperature of 24°C (18 - 32). Three children (12%) had elective open chest in view of anticipated bleeding. **Results:** The Median postoperative drainage was 127 ml, (range 10 - 1250 ml). The median postoperative use of whole blood was 95 ml (range 10 - 275), packed cell was 187 ml (range 50 - 400 ml), frozen plasma was 88 ml (range 30 - 170), platelet concentrate was 57 ml, (range 10 - 100 ml) and cryoprecipitate was median 47.5 ml, (range 30 - 80 ml). No neurological dysfunction and renal dysfunction has been observed in any of the pts. Out of 4 mortalities (16%),

only one was attributed to bleeding (4%) due to usage of ECMO. No late neurological or renal dysfunction has been observed in remaining 21 pts on follow up. **Conclusion:** High dose Tranexamic acid can be safely used in small children during complex cardiac surgery with significant reduction in post-operative bleeding and blood product usage without any higher incidence of neurological, renal dysfunction or myocardial infarction.

Keywords

Pediatric Cardiac Surgery, Bleeding, Antifibrinolytics, Tranexamic Acid, Renal Dysfunction, Neurological Dysfunction

1. Introduction

Cardiovascular surgery is always accompanied by perioperative bleeding as a result of cardiopulmonary bypass (CPB) leading to alteration of coagulation cascade [1]. The most common causes of excessive bleeding in cardiac surgical patients have been related to the interaction of blood components with the artificial surfaces of the CPB pump circuit resulting in derangements in platelet function, impairment of coagulation system and excessive fibrinolysis. Neonates, smaller children (less than ten kilo) and children with cyanotic congenital heart disease are at increased risk of bleeding after cardiac surgery. It is due to immature clotting system and more complex procedure needing longer CPB timing. The application of hypothermia in children during cardiac surgery will also result in a general slowing of proteolytic enzyme activity, reduced fibrin synthesis and reduced platelet function and thereby increases the perioperative bleeding [2] [3].

Antifibrinolytics (Aprotinin and Tranexamic acid) are routinely used during cardiac surgery in children with complex cyanotic congenital heart disease and their benefits are very well established [4] [5]. Recently Aprotinin has been withdrawn from the market in view of its multiple side effects and hence no longer available in the market. Tranexamic acid is a synthetic lysine analogue which acts by reversibly blocking the lysine binding sites of plasminogen, thus preventing its activation to plasmin [1]-[6]. The usage of Tranexamic acid has increased dramatically after withdrawal of Aprotinin since 2007. But very few randomized studies and meta analysis are available in the literature about the safety of Tranexamic acid and its effect on bleeding and reduction in blood transfusion and related complications [6]. Even very few studies are available about the safety of Tranexamic acid in neonates and smaller children [6] [7] [8]. The dose at which tranexamic acid is effective is controversial. There is a large variation in the literature regarding dosage of Tranexamic acid starting from 1 mg to 100 mg/kg in children undergoing pediatric cardiac surgery. A land mark paper from Boston Children Hospital, USA by Lin C.-Y. *et al.* [9] have recommended use of high dose Tranexamic acid. The protocol proposed by Lin C.-Y.

et al. consist of administering a bolus of 100 mg/kg of tranexamic acid to the patient after induction of anaesthesia, followed by an infusion of 10 mg/kg/h until the end of the operation and 100 mg/kg was added to the CPB priming fluid. This protocol showed greater reduction in perioperative blood loss without any increase in the side effects [9].

Objective of the Study

- 1) To determine the effect of high dose TA on blood loss and postoperative drainage during paediatric cardiac surgery.
- 2) To determine the blood product usage in the postoperative period.
- 3) To report any incidence of neurologic, renal or any other side effect of high dose TA in neonate and smaller children

2. Materials and Methods

The Institutional Ethical committee has approved this retrospective, nonrandomized study, and the approval included a waiver of informed consent. Data were collected from a retrospective review of prospectively collected data. The study period was from January 2015 to December 2015. A total of 25 patients were included in this study. Peri operative data including postoperative bleeding and total replacement of blood and blood products were obtained from anesthesia records, perfusion data base, operative notes, ICU progress notes and nurses records. The anticipated side effects of TA included neurological events, renal or myocardial infarction. The neurological events in the form of new onset of seizure either focal or generalized, Transient ischemic attacks, abnormal movements, extrapyramidal signs and symptoms, altered speech and hemiparesis were included. EEG is available in our hospital in case of any seizure activity. Renal impairment was defined as rise of creatinine more than twice the preoperative value or rise of creatinine more than 1.2 mg/dl or the need for new onset peritoneal dialysis. Myocardial infarction was defined by new ECG changes along with new onset regional wall motion abnormalities in the Echocardiogram. All data were entered into the Microsoft excel sheet for further analysis. Data are expressed as median with range and qualitative variables were expressed as a percentage. There were no control group since it was retrospective study.

2.1. Dose of Tranexamic Acid (TA)

All these infants received TA at a dosage of 100 mg/kg at the time of induction of anesthesia as a bolus and 100 mg/kg of TA was added in to the CPB pump prime. The maximum dose limit of TA was 2 g. The infusion of 10 mg/kg/hour was only used if there is ongoing blood loss with persistent coagulopathy.

2.2. Anesthesia and CPB Management

All our children received sevoflurane inhaled anesthesia along with opioids and

short acting muscle relaxants. Methylprednisolone was given at 30 mg/kg for all neonate and children needing deep hypothermic circulatory arrest. Blood prime along with Fresh Frozen Plasma (FFP) was used for all these patients and moderate to deep hypothermia was used in CPB. As a policy, our unit uses 3/16 inch tubing for arterial line in the CPB circuit in kids less than 3 kilo and 1/4 inch tubing was used for children more than 3 kilo to reduce priming volume. Ultrafiltration was used in all. Conventional ultrafiltration (CUF) was used in all and aiming for Zero balance at the end of the procedure. Cell saver was not available in our unit, hence we did not use in any of our children. Alpha stat PH management and ice around the head was used for children needing deep hypothermic circulatory arrest. Chest was left open in all neonates and children with unsatisfactory hemostasis and delayed chest closure was preferred.

2.3. Target Haemoglobin

Intraoperative haemoglobin (Hb) was maintained around 10 g/dl in all these children. Our transfusion strategy in the post operative period involves aiming for Haemoglobin of 12 g/dl in neonates and children with cyanotic congenital heart disease and 10 g/dl in children with acyanotic congenital heart disease.

3. Results

The demographic data of the population included in the study is depicted in **Figure 1** and **Figure 2**. The cardiac surgical procedure involves complete repair of Tetralogy of Fallot in 10 children, Arterial Switch Operation in 6 children, obstructed supracardiac TAPVC repair in 4, intracardiac TAPVC repair in 2, B/L BD glenn, atrial septectomy and division of MPA for tricuspid atresia in 1, correction of DORV with VSD in 1 and repair of SCIMITAR syndrome along with closure of large malaligned VSD in 1. The median CPB time was 127 minutes (range 97 - 343 min) and median cross clamp time 99 minutes (range 67 - 200 min). The median temperature of all our children in the CPB was 24 degree Celsius (18 - 32) and median Hb in the CPB was 10 g/dl (8.4 - 12).

The Median blood loss was about 127 ml (range from 10 - 1250 ml). Only one baby who underwent delayed ASO for TGA with intact ventricular septum at 35 days of life, needed ECMO after ASO in order to support untrained left ventricle had excessive bleeding. The Median postoperative blood replacement was about 193 ml (range from 10 - 1015 ml). Blood and product transfusion requirements are illustrated in **Table 1**. Whole blood transfusion was given in 22 patients (88%) at about 20 ml/kg, FFP was given in 14 children (56%) at about 18 ml/kg. Cryoprecipitate was given in 4 (16%) children at about 13 ml/kg and 10 children (40%) required platelet concentrates (PC) at about 14 ml/kg. There were four mortalities (16%) observed in this group within 30 days after surgery and only one mortality (4%) was due to excessive bleeding and drainage. The excessive bleeding was due to need of ECMO in a child after delayed ASO. The remaining three mortalities were due to pulmonary artery hypertensive crisis in 1 and low

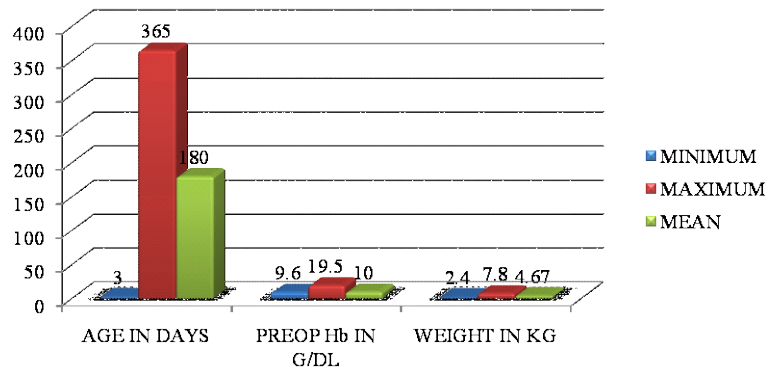


Figure 1. The Median age of the patient was 80 days (range 3 - 365 days). The median Hb level was 10 g/dl (9.6 - 19.5 g/dl). The median weight recorded was 4.67 kg (2.4 - 7.8 kg).

CASE DISTRIBUTION - DIAGNOSIS

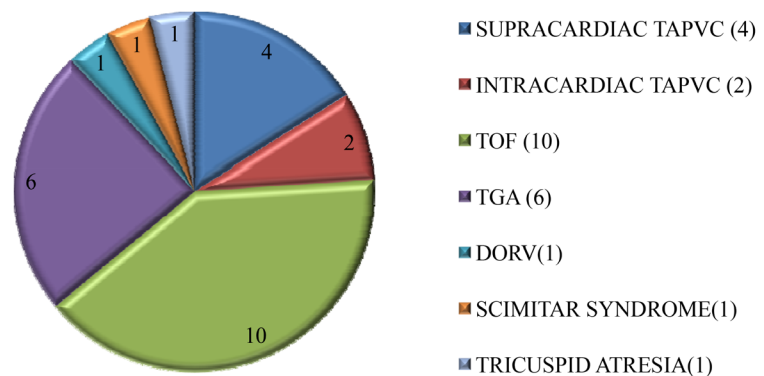


Figure 2. Preoperative cardiac diagnosis among children who underwent surgery.

cardiac output in 2 children due to ventricular failure (**Figure 3**). None of children in this study group any neurological, renal dysfunction or myocardial infarction in the postoperative period.

The median follow up was 22 months (12 months to 36 months). The complete follow up is available in 100% of alive patients. All the kids are doing well on the follow up with no onset of any new neurological or renal side effects. There are no long term mortality observed during follow up.

4. Discussion

Congenital heart defects are inherently associated with a deranged coagulation system with a pre-existing altered platelet function and altered fibrinolysis [10] [11] [12]. They are more prone for bleeding as these effects are worsened by CPB [6]. Antifibrinolytic agents are used routinely to complement the haemostasis in patients undergoing cardiac surgery.

Aprotinin was withdrawn from the market in 2007 due to high incidence of side effects and increased perioperative mortality. Some publications suggested

Table 1. Blood and product transfusion requirements in the postoperative period.

Products used	No of patients	Percentage of patients requiring product transfusion	Requirement in ml/kg
			Mean value
Whole blood	22	88%	20 ml/kg
FFP	14	56%	18 ml/kg
Cryoprecipitate	4	16%	13 ml/kg
Platelet concentrate	10	40%	14 ml/kg
PRBC	4	16%	25 ml/kg

FFP: Fresh Frozen Plasma, PRBC: Packed red blood cell.

RESULTS

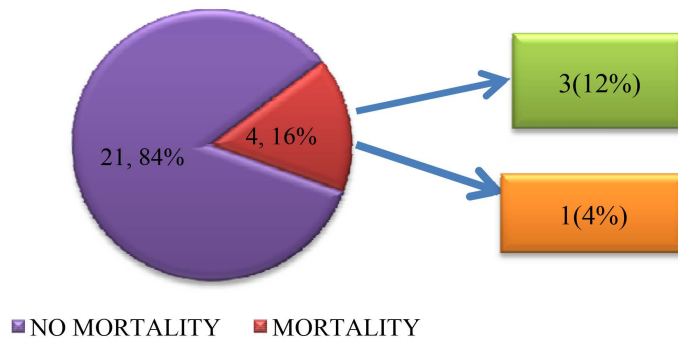


Figure 3. The Surgical outcome including 30 day mortality. NO MORTALITY: 21 (84%); MORTALITY: 4 (16%); MORTALITY DUE TO BLEEDING: 1 (4%); MORTALITY DUE TO OTHER REASONS: 3 (12%).

that the withdrawal of aprotinin has been detrimental to patients undergoing cardiac surgery due to increased adverse outcomes and use of blood products [13] [14] [15]. Since Aprotinin is no longer available, TA is now considered as the first line antifibrinolytics. TA, a synthetic analogue of the amino acid lysine, exerts its antifibrinolytic activity by competitive blockade of lysine binding sites on plasminogen to prevent its activation, and at higher concentrations, causes non-competitive inhibition of plasmin. Schindler *et al.* reported that aprotinin can be replaced with tranexamic acid because of the equal blood sparing effects, but they also indicated that the evidence accumulated at present remains insufficient to clearly estimate the benefits and risks associated with the use of tranexamic acid in congenital heart surgery [8].

There are few studies demonstrated neurological side effects with use of TA [16] [17] [18] [19]. Hence indiscriminate use of TA and especially high dose TA is a matter of concern for majority. There is major variability in dosing of TA in the currently available literature including routes of administration, amount of drug given as loading dose, pump prime, infusion and duration of infusion. The dosing of TA is important because its side effects are dose related. Few studies demonstrated increased neurological side effect if the dose of TA exceed more than 10 gram [20] [21] [22]. We have used 100 mg/kg as a bolus and 100 mg/kg

in the CPB prime with maximum dose not exceeding more than 2 g. Continuous infusion of TA at 10 mg/kg was rarely used unless there is ongoing persistent coagulopathy. We did not observe any neurological, renal or cardiac dysfunction in our 25 patients in spite using high dose of TA (maximum dose of 2 g).

The blood-conserving property of TA is uniformly reported by randomised and observational studies and in meta analyses without any increase in side effects or mortality [23] [24]. A meta analysis by Ngaage DL *et al.* [25] showed the mean chest tube drainage after cardiac surgery is less by about 283 ml (95% CI: 220 - 346, $p < 0.001$) with use of TA compared to placebo. Meta analysis also showed decrease in the risk of re-operation for bleeding by 48%, transfusion of packed red cell by 47% and use of haemostatic blood products by 67% [25].

Bleeding in neonates and infants after cardiac surgery is a nightmare for any pediatric cardiothoracic surgeon. Multiple Transfusion of blood and blood products has shown to be independent risk factor for operative mortality in multiple studies. Currently available topical hemosealants are effective but they are very expensive. Recombinant Factor VII was used in very limited centers after pediatric cardiac surgery across the world and it is not a viable option in developing nations. TA is least expensive and remains a good choice of antifibrinolytic in developing nations.

5. Conclusion

TA may be used in pediatric congenital cardiac surgery effectively at this high dose as it was found to be effective in reducing postoperative blood loss and blood product usage. Carefully designed, randomised, controlled trials are needed to explore the real efficacy and the possible side effects of TA in pediatric cardiac surgery

6. Limitations of the Study

- 1) Retrospective study
- 2) Smaller number of children
- 3) No control group to compare the real efficacy of high dose TA
- 4) Liberal use of blood and product transfusion to maintain Hb value of 12 g/dl in the postoperative period despite usage of TA, so the genuine need for postoperative blood product usage after TA was masked.

Funding

This study was not funded any one.

Conflict of Interest

No.

Ethical Approval

All procedures performed in studies involving human participants were in ac-

cordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

This was a retrospective observational studies, hence Informed consent was waived off by our ethical Committee.

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Abbreviations

ASO: Arterial Switch Operation

BD Glenn: Bidirectional Glenn shunt

CPB: Cardio Pulmonary Bypass

DORV: Double Outlet Right Ventricle

ECG: Electrocardiogram

EEG: Electroencephalogram

ECMO: Extra Corporeal Membrane Oxygenation

FFP: Fresh Frozen Plasma

Hb: Haemoglobin

ICR: Intra Cardiac Repair

ICU: Intensive Care Unit

MPA: Main Pulmonary Artery

PS: Pulmonary Stenosis

SCIMITAR syndrome: Anomalous Right pulmonary venous drainage in to Inferior Vena Cava, associated with hypoplastic Right lung

TA: Tranexamic Acid

TOF: Tetralogy of Fallot

TAPVC: Total Anomalous Pulmonary Venous Connection

TGA: Transposition of Great Arteries

VSD: Ventricular Septal Defect