(9) ROLE OF TRANEXAMIC ACID FOR REDUCING BLOOD LOSS IN TETRALOGY OF FALLOT

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BACKGROUND: Antifibrinolytic agents are used to reduce post-operative blood loss during cardiac surgeries. Paucity of literature on tranexamic acid in patients undergoing tetralogy of fallot repair encouraged us for this study at a tertiary cardiac care center. Administration of antifibrinolytic agent tranexamic acid decreases bleeding and transfusions during post-operative period.

METHODS : Sixty pediatric patients undergoing surgical repair for tetralogy of fallot were divided into two groups. The control (Group-A) did not receive the drug while the study group (Group-B) received IV tranexamic acid at pre-incision, during priming and heparin reversal at 10 mg/kg. Blood loss, need for supplementation of blood and blood products, coagulation parameters and re-exploration rate were compared between the groups.

RESULTS : Both groups had comparable demographic parameters (age, weight, and body surface area and tetralogy of fallot characteristics). Tranexamic acid treated patients experienced lesser blood loss ($p<0.0003$), need for PCV ($p<0.0001$) or Fresh Frozen Plasma (FFP; $p<0.0001$). Improved coagulation parameters [increased Fibrinogen content ($p<0.01$) and platelets ($p<0.01$); decreased activated clotting time ($p<0.01$) and fibrin degradation product ($p<0.01$) were also seen in drug treated patients.

CONCLUSION: Tranexamic acid was effective in reducing post-operative blood loss with improved coagulation parameters. We therefore advocate its routine use for tetralogy of fallot repair surgeries in pediatric patients.

KEYWORDS: Tetralogy of Fallot, Congenital Heart Diseases, Cardio Pulmonary Bypass, Ventricular Septal Defect.

INTRODUCTION:

Children with congenital cyanotic heart diseases undergoing corrective cardiac surgery are normally at high risk of excessive post-operative bleeding. Surgical correction of Tetralogy of Fallot consist of Ventricular Septal Defect (VSD) closure and right ventricular infundibular resection, so that all the blood from right ventricle can be pumped into pulmonary artery.

Risk of excessive bleeding during and after cardiac procedure is due to hematological abnormalities like Polycythemia, Thrombocytopenia, Thrombocytopathy, Coagulation factor deficiencies, excessive fibrinolysis and disseminated intravascular coagulation.[1] Use of Heparin, blood and blood product transfusion and exposure to cardiopulmonary bypass (CPB) increases risk of bleeding.[2] Apparently, use of such techniques increase the cost of surgery, lead to inappropriate usage of human blood and expose the patients to various immunological reactions related to blood transfusion.[2]

The perioperative physician plays an important role in such cases. Antifibrinolytic agents are commonly administrated prior to surgery. Prophylactic administration of antifibrinolytic drug tranexamic acid (TA) decreases bleeding and transfusions after cardiac surgeries. Tranexamic acid is proved to be efficient with promising results in controlling post-operative bleeding in patients of Tetralogy of Fallot (TOF) undergoing intra cardiac repair.[3]

Tranexamic acid is a lysine analog that competitively binds to the lysine binding sites of plasmin and plasminogen. It has been reported to inhibit fibrinolysis with six to ten fold higher potency than any other antifibrinolytic drug.[4]

Since excessive bleeding may complicate cardiac surgery and is likely to be associated with increased morbidity and mortality[5], the current study was designed to assess the effect of tranexamic acid at a loading dose 10 mg/kg IV pre-incision, 10mg/kg in priming solution, and 10mg/kg IV after protamine. The influence on blood transfusion, thromboembolic events and mortality in patients undergoing intra cardiac repair for the correction of TOF were also evaluated.

MATERIALS AND METHODS:

The case-control study under report was conducted during July 2012 to February 2013 at U. N. Mehta Institute of Cardiology and Research Centre, Ahmedabad after approval of institutional Ethics Committee and informed consent from parents of the patients. The sample size was determined using the standard formula using Z_{crit}: (Standard Normal Deviate) corresponding to Selected significance criteria (1.96) and Z_{pwr}: (Standard Normal Deviate) corresponding to selected statistical power (0.84).

Sixty children with tetralogy of fallot undergoing primary intra cardiac repair in the age range of 2 to 15 years were randomly assigned either to no treatment (Group-A) or treatment [TA (Torrent Pharma; Gujarat) at a loading dose 10 mg/kg IV pre-incision, 10mg/kg in priming solution, and 10mg/kg IV after protamine; Group-B]. The patients with renal impairment, congenital bleeding disorders or past neurological events were excluded from the study. No

patient in any of the groups experienced cyanotic spells and their hemoconcentration was not adjusted before surgery.

TA administration was initiated after induction of anaesthesia at a dose of 10 mg/kg I.V. followed by the same dose in priming solution and the same dose was continued I.V. after protamine for heparin reversal.

Anaesthesia and CPB management was similar in both the groups as per the institutional protocol except for the administration of TA in group B. The intra cardiac repair was performed by the same surgical team to rule out individual variation in surgical technique and to reduce variations in the post-operative blood loss.

Anaesthesia was induced with inj. Ketamine (Themis Pharma, Uttarakhand) and inj. Fentanyl (Troikaa Pharm, Gujarat), Inj. Midazolam (Ranbaxy laboratories, Himachal Pradesh) and Inj. Vecuronium (Health Biotech, Himachal Pradesh) for muscle relaxation. Anaesthesia was maintained on air +O2+ Fentanyl+ Vecuronium + Sevofluarane (Aesica queen Borough Ltd, U.K).

CPB management was performed with membrane oxygenator (Edwards Life Sciences, USA; Vital Oxygenator), moderate hypothermia (28°C) with non-occlusive roller pumps (Stockert SIII). Bypass circuit was primed with Ringer lactate solution (20 ml/kg), Sodium bicarbonate [7.5% (W/V) at 1ml/kg], Mannitol [20% (W/V), 0.5 gm/kg] and heparin (100 units/kg). Blood was added if hematocrit on bypass fell below 24%.

Duration from protamine administration to sternal closure was noted as an indirect assessment of coagulation status. A separate and the same intensivist team managed the patients during post-operative period. The post-operative bleeding, blood and blood product administration was especially managed by them. Post- operative blood loss was recorded for 24 hours. Usage of blood, blood products were noted during the post-operative period of 24 hours.

Blood samples were collected at a six hourly interval post-operatively to test coagulation parameters including platelet count, activated clotting time, fibrinogen and fibrin degradation product. Re-exploration rate in both the groups was also recorded.

Pre- and Intra- operative parameters like Sternal closure time (Min), Post-operative hematocrit (%), Urine on CPB (C), Cross clamp time (min), Pre-operative hematocrit (%), On CPB hematocrit (%) and CPB time (min) were noted. Post-operative coagulation tests like Activated clotting time (Sec), Fibrinogen (g/L), Fibrin degradation product (ng/ml) and Platelet count (Lacs) were also performed. Renal and cerebral complications were observed.

Results were expressed as mean ± standard deviation. Mann Whitney ‘U’ test and Independent ‘t’ test were performed using SPSS v 20.0. $p < 0.05$ were considered as significant.

RESULTS :

Sixty (60) children undergoing corrective surgery for TOF were equally divided into two groups. Group A (Control) did not receive any treatment while Group B (Study group) received Tranexamic acid treatment. Demographic data of children from both the groups were comparable with age

(Range: 2 to 15 years), weight and body surface area (BSA; Table-1). The patients with good size pulmonary artery was similar in both the groups [(Group A; N=20); (Group B; N=22). Hypoplastic main pulmonary artery was observed in 4 patients in Group A and 5 patients in Group B. Hypoplastic LPA/RPA was observed in 6 patients in Group A and 3 patients in Group B (Table-1). Comparison of post-operative observations are presented in Table-2. Tranexamic acid treated patients experienced significantly reduced blood loss ($p < 0.0003$), use of PCV ($p < 0.0001$) and use of Fresh Frozen Plasma (FFP; $p < 0.0001$) while platelet concentration was similar between the groups. Re-exploration was required in one patient in the control group as opposed to none in the treatment group.

Amongst the pre- and intra- operative parameters, Group B (Drug treated) demonstrated a significant decrease in cross clamp time (Fig.-1; $p<0.01$) and sternal closure time (Fig.-1; $p < 0.01$) while time on CPB machine was similar between controls and the study group (Fig.-1).
There was an increase in in Post-operative hematocrit (Fig.-2; $p < 0.01$) in study group as compared to controls. On the other hand, Pre-operative hematocrit, On CPB hematocrit were similar in both these groups (Fig.-2). The urine output on CBP was similar between the two groups (Fig.-3).

Post-operative coagulation tests at 6 hours demonstrated that the drug treated group (Group B) exhibited a significant increase in Fibrinogen content (Fig.-4; $p < 0.01$), platelet count (Fig.-4; $p < 0.01$) and a significant decline in fibrin degradation product (Fig.-4; $p < 0.01$) and activated clotting time (Fig.-5; $p < 0.01$) and as compared to the control.

DISCUSSION:

Coagulation abnormalities during cardiac surgery has been widely reported. Platelet dysfunction and fibrinolysis are important causes of increased post-operative blood loss after cardiac surgeries performed under CPB.[6] Congenital heart disease patients have unbalanced coagulation system with preceding platelet dysfunction and amplified fibrinolysis; such cases are more prone to post-operative bleeding.[7]

During the natural process, fibrinogen is synthesized by liver and cleaved by thrombin to form fibrin monomers. Factor XIIIa cross-links the fibrin monomers providing stability to fibrin. Plasminogen binds to fibrinogen before its conversion into fibrin. Fibrinolysis inhibitors bind to plasmin and interfere with its ability to cleave fibrin. Hence these inhibitors are contraindicated in intravascular coagulation clots.[8] Antifibrinolytic agents such as tranexamic acid have been successfully employed in patients undergoing cardiac surgeries.

Patients with congenital cyanotic heart disease are known to benefit from anti fibrinolytic agents such as ε-aminocaproic acid which has been reported in several studies to reduce post-operative blood loss.[9,10] Tranexamic acid is ten times more potent than ε-aminocaproic acid as an anti fibrinolytic agent, with more effective binding to plasminogen. [11,12]

Reichert et al[13] studied TA in 88 children administered with a single dose of 50 mg/kg and observed no benefit in 64 non cyanotic patients in terms of reduction in bleeding or transfusion

requirements. Efficacy of TA was studied by Chauhan et al[3] with different dose regimes. They found that single bolus of TA is least effective. Sustained anti fibrinolysis was produced by using TA before skin incision, with additional dose on CPB and another dose after weaning from CPB.[7,14]

Tranexamic acid is known to reduce the risk of death in adults undergoing cardiac surgeries as compared to aprotinin.[15] In addition, it has also been reported to increase the risk of seizures and persistent atrial fibrillation in adults.[15] However, the authors were unable to find relevant literature on the use of tranexamic acid especially in intracardiac repair for TOF in pediatric patients. The current study therefore is the first report from India for use of tranexamic acid in pediatric TOF repair surgery. Possibility of creation of a hyper-coaguable state is of a great concern to anaesthetists. Cerebral, pulmonary, mesenteric and retinal thrombosis have been reported so far in literature.[16]

Use of tranexamic acid in the current case-control study has very clearly demonstrated a significant reduction in blood loss obviating a reduced need for PCV transfusions and FFP similar to Brown et al.[17] In addition, the current study showed a significant improvement in coagulation parameters as reflected by a decline in activated clotting time and fibrin degradation product with the use of tranexamic acid.

Thus, the results of the current case-control study demonstrate that TA is associated with allogenic blood sparing with the current protocol [10 mg/kg IV before incision, 10 mg/kg in priming solution and 10 mg/kg IV after protamine (for heparin reversal)] similar to the study reported by Casati et al.[18]

No thrombotic events or other complications were encountered in this study. The authors of the current study therefore understand that the coagulation parameters are likely to return to normal in 12 hours post-operatively.[19]We infer that tranexamic acid effectively reduces the blood loss, results into improved coagulation parameters at the current administrative dose in pediatric patients undergoing TOF repair. The current report however, is based on a series with smaller number of patients and demands studies with a large number of patients.

CONCLUSION :

Tranexamic acid at a dose of 10mg/kg I.V. is highly effective as antifibrinolytic agent in children with TOF undergoing intra cardiac repair. It effectively reduces post-operative blood loss and transfusion in the form of blood, fresh frozen plasma, platelets. Routine use of I.V. tranexamic acid with a protocol of (i) at pre-incision, (ii) during priming and (iii) heparin reversal at 10 mg/kg is advocated.

Table 1- Demographic data of two groups

Demographic data/Diagnosis	Group A (N=30) Mean±SD	Group B (N=30) Mean±SD	p Value
Age (yrs.) Mean±SD	5.97±3.76	5.50±3.71	0.6278
Male/Female ratio	16/14	20/10	
Weight (kg)	13.83±6.88	13.83±6.68	1.0000
BSA (m^2)	0.58±0.19	0.55±0.15	0.5000
Diagnosis			
TOF with good size PA	20	22	-
TOF with hypo plastic MPA	04	05	-
TOF with hypo plastic LPA/RPA	06	03	-

Group A and group B were comparable in terms of children age range (2 to 15 years), weight, and body surface area.

Table 2- Postoperative observations in two groups

Postoperative observation	Group A(N=30) Mean±SD	Group B(N=30) Mean±SD	p-Value
Blood loss (ml/kg/24 hrs.)	33.70±16.78	20±9.78	0.0003
PCV used (ml/kg/24 hrs.)	20.49±7.70	13.70±4.24	0.0001
FFP used (ml/kg/24 hrs.)	18.30±4.71	12.56±2.42	0.0001
Platelet concentration (ml/kg/24 hrs.)	6.80±1.99	6.50±1.78 (NS)	0.5407
Re-exploration	(1/30) (3.33)	(0/30) (0) (NS)	-

Post-operative data is in form of blood loss, usage of blood, blood products, which shows group B had lower blood loss and it is reflected as lower usage of blood, blood products in group B compared to group A.

Re-exploration rate was low in group B.

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