

The Efficacy of Tranexamic Acid Versus Epsilon Amino Caproic Acid in Decreasing Blood Loss in Patients Undergoing Mitral Valve Replacement Surgery

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Abstract: Open heart surgeries under cardiopulmonary bypass are associated with excessive perioperative bleeding that often requires re-exploration. Antifibrinolytics like epsilon aminocaproic acid and tranexamic acid are widely used to control bleeding. There is paucity of literature on studies to reduce blood loss and blood transfusion following mitral valve replacement surgeries. The aim of this study was to compare incidence of re-exploration, blood loss and blood transfusion following mitral valve replacement surgeries in patients who were administered either tranexamic acid or epsilon amino caproic acid. However their efficacy has not been studied in mitral valve replacement surgeries. This is a prospective, randomized, double blind study performed among sixty patients of either sex in the age group of 18 to 60 years scheduled for mitral valve replacement surgeries. They were randomly allocated into two groups, Group 1 (TA n=30) tranexamic acid 20 mg/kg body weight diluted in 20ml syringe over 20 min as bolus at time of induction of anaesthesia, infusion of 2mg/kg/hr started continued throughout surgery and continued till 6 hour post operatively in recovery room. Group 2 (EACA n=30) epsilon amino caproic acid 100 mg/kg body wt bolus diluted to 20 ml syringe over 20 min as bolus at time of induction of anaesthesia, infusion 20mg/kg/hr started continued throughout surgery and continued till 6 hour post operatively in recovery room. After admission to intensive care unit total blood loss, transfusion requirements during the first 24 hours and other complications were recorded. In our study we found that mean post operative blood loss in tranexamic acid group 416+47.74 (ml) which is lower than epsilon amino caproic acid group 489+42.12 (ml) that is statistically significant. 16 out of 30 patients in TA group i.e. 53.3% patients received transfusion, where as in EACA group 21 out of 30 patients i.e. 70% patients received transfusion. The total transfusion requirements, total donor unit exposure and financial cost of blood components are less in the tranexamic acid group. Prophylactic tranexamic acid effectively reduces perioperative blood loss in mitral valve replacement surgery.

Keywords: Epsilon Amino Caproic Acid, Mitral Valve Replacement, Post Operative Bleeding, Tranexamic Acid

1. Introduction

Cardiopulmonary bypass (CPB) is a double-edged sword. Without it, corrective cardiac surgery would not be possible in the majority of children with congenital heart disease. In 1953, John Gibbon performed the first successful open-heart

operation using a heart-lung machine in human patient. Blood requirements per cardiac case in the early 1950's were 20 to 30 units [1]. Despite continuous advances improving the safety of cardiac surgery, excessive bleeding requiring transfusion of blood components after CPB is still one of the main causes of postoperative morbidity [2]. The nonendothelial surfaces of the CPB circuit cause contact activation of the coagulation

cascades and of platelets, despite the use of heparin. Thus, CPB is associated with several alterations in the haemostatic mechanisms including increased fibrinolysis, decreased platelet numbers and function, dilution of clotting factors, and the residual effects of heparin or excess protamine. Increased fibrinolytic activity and platelet dysfunction have been identified as important factors of postoperative bleeding [3]. In cardiac surgery postoperative bleeding is associated with an increased incidence of surgical re-exploration to identify the source of bleeding. Increased use of blood causes significant morbidities such as renal failure, sepsis, arrhythmias, prolonged requirement for mechanical ventilatory support, longer hospital stay and increased mortality [4]. Public apprehension of transfusion related communicable diseases particularly AIDS, modulation of the immune response, and increased risk of postoperative infection, the problems of occasional shortages of donor blood and increasing costs [1], has refocus the attention of cardiac surgeons on the importance of haemostasis to minimize the need for, and therefore the risk of blood transfusion. These risks increase proportionately to the number of donors to which the recipient is exposed.

The use of drugs to reduce bleeding in the post-operative period of CPB assisted heart surgery has been studied since the report by Mammem et al. with aprotinin in 1968 [5]. From 1980, there has been growing interest in methods to minimize the exposure to blood and its derivatives in the peri-operative period, as it was discovered that HIV, hepatitis etc could be transmitted by transfusions [4]. At present three antifibrinolytic agents of which two synthetic (epsilon aminocaproic acid, tranexamic acid) and one natural (aprotinin) that are available for clinical use. The most thoroughly evaluated antifibrinolytic agent is aprotinin. Its effectiveness in reducing postoperative haemorrhage has been established in more than 40 randomized clinical trials and 2 meta-analyses. However, aprotinin is expensive. In addition, there are concerns about potential thrombosis related side effects and allergic reactions with antifibrinolytic agents. For these reasons, prophylactic use of aprotinin is often limited to patients at high risk for bleeding (eg, reoperations) or those for whom transfusions are not acceptable because of religious beliefs (eg, Jehovah's Witnesses). The FDA required new labeling for aprotinin, focusing on indications for use, added a warning about renal dysfunction, revised a warning about anaphylactic reactions, and added a contraindication. On October 19, 2007, a communication to the FDA from the Data Safety Monitoring Board of a Canadian randomized study evaluating the safety of antifibrinolytic therapies stated that the trial was being halted because of a higher mortality trend in the aprotinin arm. Reacting to this negative finding, the FDA announced the suspension of aprotinin marketing in 2007 [6].

Epsilon aminocaproic acid (EACA) and tranexamic acid (TA) are antifibrinolytic agents that are inexpensive and that do not have the increased risk of anaphylaxis of aprotinin upon re-exposure. Treatment with either EACA/ TA prior to CPB has been shown to reduce blood loss in perioperative period following open heart surgery [1-4]. The use of

tranexamic acid in cardiac operations has been reported in more randomized trials than epsilon aminocaproic acid. A placebo control group was not used for this study since the efficacy of the drugs has been established in the literature. So it would have been unethical to conduct placebo control study. Thus tranexamic acid was chosen as the synthetic antifibrinolytic to compare against epsilon aminocaproic acid. The purpose of the present study was therefore, to compare the efficacy of tranexamic acid vs epsilon aminocaproic acid on postoperative bleeding and transfusion requirements following mitral valve replacement surgery.

2. Material and Methods

This study was undertaken after an institutional approval by the Committee on Human Research Publications and Ethics was obtained. The study was conducted from November 2013 to May 2014. Informed consent was obtained from 60 patients. The study population consisted of American Society of Anaesthesiologists (ASA) physical status III; male and female adults between the ages of 18-60 years scheduled for mitral valve replacement surgery under general anaesthesia.

2.1. Study Design

This study was a prospective, randomised and double-blinded clinical comparison. The Sample size for the study was 60 generated using a sample size calculator. The study Participants were randomly divided into two groups by a computer generated randomization table. Group 1 (TA n=30) tranexamic acid 20 mg/kg body wt diluted to 20 ml of NS over 20 min as bolus at time of induction of anaesthesia, and infusion of 2mg/kg/hr started continued throughout surgery till 6 hour post operatively in recovery room. Group 2 (EACA n=30) epsilon amino caproic acid 100 mg/kg body wt bolus diluted to 20 ml of NS over 20 min as bolus at time of induction of anaesthesia, & infusion 20mg/kg/hr started continued throughout surgery till 6 hour post operatively in recovery room. Both the drugs were coded to enhance blinding.

2.2. Inclusion Criteria

Inclusion criteria for the study were ASA class III; age range 18–65, either sex, posted for elective mitral valve replacement surgery, preoperative hemoglobin >10 gm %, haematocrit >30%, normal coagulation profile including PT and INR.

2.3. Exclusion Criteria

Exclusion criteria for the study included patients who were morbidly obese; Heart rate <50 beats per minute (bpm), basal SBP<100 mmHg, bleeding diathesis, allergic reaction to anti fibrinolytic drugs, deranged coagulation profile PT<75% or INR>2, thrombosis, urinary tract bleeding, Pre operative renal failure (serum creatinine >2), Pregnancy, Patient on anti platelet treatment within 7 days of surgery, Redo surgery, emergency operation and patients refusal.

2.4. Pre-Surgical Protocol

The day prior to surgery all patients underwent a preanesthetic evaluation with special consideration to elicit any new change, previous anaesthetic history and drug sensitivity. Information collected included weight, nutritional status, airway assessment by the Mallampatti scoring system; a detailed examination of the respiratory; cardiovascular and central nervous system. A preoperative routine investigations such as haemoglobin, haematocrit, total lymphocyte count, differential lymphocyte count, serum electrolytes, blood group/Rh typing, blood urea nitrogen, serum creatinine, fasting blood sugar, chest radiography, Echo and electro-cardiogram in all patients. Patients were advised to fast the night prior to surgery.

2.5. Surgical Protocol

After patient identification a short preoperative history was taken; clinical examination and routine investigations were rechecked in all patients. Study objective and procedure were explained to the participants and a written informed consent was obtained from each participant. Baseline vitals like heart rate, rhythm, non invasive blood pressure monitoring (NIBP), SpO₂, respiratory rate were monitored before induction. A peripheral line intra venous (IV) line was established with 20G IV cannula and Ringer Lactate infusion was started. Premedication with IV Fentanyl 3 µg/kg and Midazolam 0.05mg/kg was administered. Central venous, radial / femoral arterial lines were established under local anaesthesia. Invasive blood pressure as well CVP was monitored. Study drugs given as above mentioned as per protocol by anaesthetist who is blinded for study.

Patient was induced with inj. Thiopental 5-7mg/kg. Neuromuscular blocked was achieved and maintained with vecuronium 0.15mg/kg. Intubation was done with the appropriate sized cuffed endotracheal tube. After inflating the cuff and securing the tube, controlled mechanical ventilation was started and anaesthesia was maintained on O₂ with inhalational anaesthetic agent 0.6% -1.2% Isoflurane on semi closed circle system with CO₂ absorber and flow rate of 3 lit/min (Datex ohmeda). Fentanyl, midazolam, vecuronium were administered as per needs.

Heparin was given at a dose of 300 U/kg and supplemented as necessary to maintain ACT>400 sec while on Cardio Pulmonary Bypass. Pump prime consisted of 1200ml balanced electrolyte solution and 500ml of tetra starch containing 25meq of sodium bicarbonate and 5000 units of heparin mannitol 100 ml and, lasix 1 mg/kg. CPB was maintained with roller pump utilizing a membrane oxygenator. All Patients

underwent standard nonpulsatile normothermic or mildly hypothermic (28°C to 32°C) Cardio Pulmonary Bypass. Myocardial protection was induced with 15-20 ml/ kg of cold high potassium cardioplegia (16 mmol potassium in 20 ml plegiocard solution) through the aortic root after aortic occlusion. After mitral valve replacement, closure of left atrium done & rest time patient is gradually weaned from bypass. Inotropes, vasopressors, vasodilators etc were administered as per needs. Heparin was neutralized with protamine 1.5 mg/100 IU heparin administered. Blood samples was collected for Hb, ABG and electrolytes at the following time points after induction, immediately after heparin administration, following neutralization with protamine, postoperatively every hourly till 6 hours, at 9, 12, 18, and 24 hour. Activated clotting time (ACT) was performed at baseline, after heparine administration, after protamine titration, post operatively, if bleeding is >200ml/hour. Patient monitored as per standard hospital protocol for cardiac surgery throughout perioperative course. After skin closure patient shifted to recovery room, there drain bottles attached to slow suction. Patients were mechanically ventilated for 3-4 hour. If patient is without any complication and stable then weaned off from the mechanical ventilation.

2.6. Parameters and Statistical Analysis

Summary statistics of patient demographic for both the groups were reported as means ± Standard deviation (SD). Data for continuous parameters was collected and compared between Group I and Group II. Statistical analysis was done by unpaired t-test whilst non normalized data were compared using Mann Whitney test. p value less than 0.05 was considered as statistical significant. Data was analyzed by statistical software SPSS 16.

3. Results

A comparison of the demographic profile of the study groups are as shown in Table 1. No significant difference was observed in the mean age for group 1TA patients (29.3±10.35 years) when compared to those in group 2 EACA (32.4±11.8 years) (p=0.284). The male to female ratio of group 1TA was 1:1.5 whereas that of group 2 EACA was 1:2.6 (p=0.34). The average weight was 42.9±12.5 kg and 43.5±6.89 kg in groups 1 and 2 respectively (p=0.8161). The average height in group I was 153±12.70 cm and group II was 155.86±11.05 cm (p=0.5324). The average body mass index was 18.00±3.49 and 17.98±1.90 in group 1 and 2 respectively (p=0.625).

Table 1. Comparison of TA versus EACA (preoperative demographic profile).

Parameter	GROUP 1 TA (n=30) Mean ± SD	GROUP 2 EACA (n=30) Mean ± SD	P
Age (yrs)	29.3±10.35	32.4±11.8	0.284
Sex ratio M/F	1:1.5	1: 2.6	0.344
Weight (kg)	42.9±12.5	43.5±6.89	0.8161
Height (cms)	153±12.70	155.86±11.05	0.5324
Body mass index	18.00±3.49	17.98±1.90	0.625

Preoperative parameter

Table 2. Shows preoperative investigations of patients in both the groups.

Parameter	Group 1 (TA n=30) Mean ± SD	Group 2 (EACA n=30) Mean ± SD	p
Hb %	11.6±1.4	11.4±1.01	0.44
INR	1.14±0.21	1.13±0.11	0.835
KFT Blood urea	25.03±8.31	24.80±7.29	0.908
KFT Serum creatinine	1.07±1.51	0.7767±0.17	0.295

The table 2 shows preoperative Hb%, INR and kidney function test. There were no statistically significant preoperative intergroup differences with respect to Hb%, INR and kidney function test (p>0.05).

Intra operative Parameter

Table 3. Comparison of TA versus EACA (Intra operative coagulation states and duration of cardiopulmonary bypass).

Parameter	Group 1 (TA n=30)	Group 2 (EACA n=30)	p
	Mean ± SD	Mean ± SD	
ACT Baseline (sec)	108.45 ± 26.63	114.13 ± 20.03	0.364
ACT post Heparin (sec)	610.38 ± 142.30	613.20 ± 99.19	0.929
ACT after protamin (sec)	116.61 ± 18.60	117.31 ± 9.88	0.858
Duration of bypass (mins)	72.74 ± 27.07	71.78 ± 32.26	0.902

Intra operative parameters like coagulation states and duration of cardiopulmonary bypass are presented in table 3. It shows that activated clotting time ACT (baseline, post heparin and after protamine titration) not significant in both the groups (p>0.05). Mean duration of bypass in TA group 72.74 ± 27.07 mins which does not vary significantly from that in EACA group 71.78 ± 32.26 mins (p=0.902).

Post operative blood loss at 24 hours

Table 4. Comparison of TA versus EACA (mean postoperative blood loss at 24 hours).

Parameter	Group 1 TA (n=30)	GROUP 2 EACA (group)	P
	Mean ± SD	Mean ± SD	
Total Chest Drain After 24 Hour (ml)	416.00 ± 47.74	489 ± 42.12	0.0001

Table 4 shows mean postoperative blood loss at 24 hours (measured in terms of amount of blood collected in chest drain) in both groups. Patients in TA group significantly lower postoperative blood loss at 24 hour as compared to patients in EACA group. Mean postoperative blood loss at 24

hour in group 1 (TA) 416.00 ± 47.74 ml which is much lower than post operative blood loss at 24 hour in group 2 (EACA) 489 ± 42.12 ml (p=0.0001) which is statically significant (p=0.0001).

Post operative blood loss

Table 5. Comparison of TA versus EACA (mean postoperative blood loss in ml).

BLOOD LOSS (ml)	Group 1 TA	Group 2 EACA	p
	Mean ± SD	Mean ± SD	
1 hr	63.66±17.0	79.33±10.80	0.0001
2 hr	53.33±12.95	71.00±10.28	0.0001
3 hr	42.66±11.72	52.33±17.74	0.016
4 hr	35.33±12.24	44.00±9.32	0.003
5 hr	29.00±12.68	39.33±9.80	0.001
6 hr	39.33±9.80	49.66±12.72	0.001
9 hr	39.00±10.61	39.33±8.68	0.895
12 hr	38.66±8.19	37.66±7.73	0.629
18 hr	36.33±8.50	35.66±11.35	0.798
24 hr	38.66±8.19	40.66±9.44	0.385
Total	416.00±47.74	489.00±42.12	0.0001

In table 5 analysis of blood loss at timely interval as per study protocol. The blood loss is recorded at hourly interval up to first 6 hour thereafter at 9, 12, 18 and 24 hours. Mean blood loss at specified interval in each group is shown in table no 5. The mean blood loss was higher in EACA group

postoperatively as compared to TA group up to first 6 hrs. Statistically this difference is highly significant. After 6 hours though mean blood loss is higher in EACA group as compared to TA but the difference is not statistically significant. These trends are plotted in graph 1.

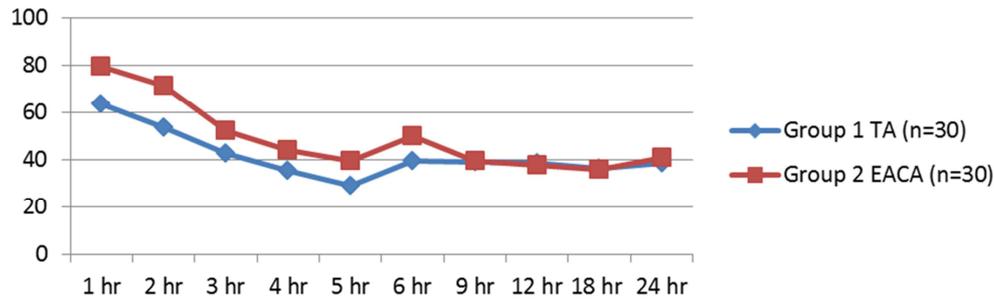


Figure 1. Postoperative blood loss trends in both groups.

The number of units of whole blood or blood component transfused

Table 6. Comparison of TA versus EACA (units of blood, blood components transfused/all patients).

Total transfusion (in Units)	Group 1 (TA n=30)	Group 2 (EACA n=30)	p (Mann Whitney test)
	Median (interpercentile range 25 th -75 th)	Median (interpercentile range 25 th -75 th)	
Blood	0.45 ± 0.62	0.86 ± 0.87	0.0481
FFP	0.48 ± 0.76	0.68 ± 0.71	0.2876
Platelet	0.35 ± 0.71	0.65 ± 0.85	0.1435

Table 6 demonstrates the comparison of number of units of whole blood or blood component transfused/all patients between two groups. There is a significant decrease in number of units of whole blood transfusion requirement in TA group as compared to EACA group as shown in table above. TA group received on an average 0.45±0.62 unit/per patient as compared to EACA group 0.86±0.87 units per patient. The number of units of FFP and platelet required per patient did not vary significantly among two groups

Number of patients requiring transfusion of blood/blood products

Table 7. Shows number of patients requiring transfusion of blood/blood products.

Parameter	Group 1 TA (n=30)	Group 2 EACA (n=30)
	Mean ± SD	Mean ± SD
Number of patients receiving transfusion	16 (53.3%)	21 (70%)

From table 7 it is seen that 16 out of 30 patients in TA group i.e. 53.3% patients received transfusion where as in EACA group 21 out of 30 patients i.e. 70% patients received transfusion.

Hemoglobin and INR on second day

Table 8. Focuses on variation between two groups in regard to Hb% on second day and INR.

Parameter on day 2 (at 24 hrs)	Group 1 (TA n=30)	Group 2 (EACA n=30)	P
	Mean ± SD	Mean ± SD	
Hb %	10.74±1.23	9.95±1.16	0.013
INR	1.41±0.26	1.33 ±0.28	0.299

Table 8 it is reveal that mean Hb% of patients in TA group (10.74±1.23) was slightly better as compared to mean Hb% of patients in EACA group (9.95±1.26) on second day. The difference is statistically significant (p < 0.05). From above

table it is seen that INR on day 2 in group 1 TA is 1.41±0.26 and in group 2 is 1.33 ±0.28. The difference is not statistically significant.

Re-exploration: None of the patient in either group has been re explored.

Adverse outcome: No complications like kidney failure, stroke, AMI were observed in either group. Only 1 patient in EACA group had convulsions.

Pulse rate

Table 9. Comparison of TA versus EACA (pulse rate).

Pulse rate (per min)	TA group	EACA group	p
	Mean ± SD	Mean ± SD	
Baseline	89.50±8.50	89.40±10.89	0.969
Prebypass	89.26±7.62	90.73±5.95	0.410
Postbypass	83.93±6.79	84.26±7.11	0.853
1 hr	101.90±9.92	101.33±5.21	0.783
2 hr	99.20±6.77	99.53±5.06	0.830
3 hr	84.86±5.05	86.30±5.19	0.283
4 hr	87.03±5.80	85.36±15.74	0.589
5 hr	82.13±2.96	83.40±6.11	0.311
6 hr	80.10±13.94	82.26±6.37	0.442
9 hr	82.66±7.29	84.40±5.73	0.311
12 hr	83.66±4.87	82.93±5.27	0.578
18 hr	79.46±4.29	80.90±4.39	0.207
24 hr	77.26±3.61	77.13±4.10	0.894

The pulse rate is recorded at hourly interval up to first 6 hour thereafter at 9, 12, 18 and 24 hours. Mean pulse rate at specified interval in each group is shown in table no 10. Pulse rate did not vary significantly between two groups showing hemodynamic stability.

Systolic blood pressure

Table 10. Comparison of TA versus EACA (systolic blood pressure).

	TA group	EACA group	p
	Mean ± SD	Mean ± SD	
Baseline	115.86±9.06	115.23±6.80	0.761
Prebypass	110.73±6.44	112.93±6.53	0.194
Postbypass	105.80±7.46	105.53±5.32	0.874
1 hr	102.70±5.74	101.06±7.36	0.342
2 hr	114.86±7.32	116.76±5.92	0.274
3 hr	102.96±2.83	102.93±8.61	0.984
4 hr	112.00±4.69	112.26±4.80	0.829
5 hr	113.46±4.54	111.33±5.64	0.112
6 hr	114.13±7.53	113.60±7.30	0.782
9 hr	112.13±4.54	110.56±5.17	0.218
12 hr	112.06±4.37	111.96±5.49	0.938
18 hr	110.93±4.09	111.80±4.31	0.428
24 hr	109.50±3.68	110.20±4.99	0.539

The systolic blood pressure is recorded at hourly interval up to first 6 hour thereafter at 9, 12, 18 and 24 hours. Mean systolic blood pressure at specified interval in each group is shown in table no 11. Systolic blood pressure did not vary significantly between two groups showing hemodynamic stability.

Diastolic blood pressure

Table 11. Comparison of TA versus EACA (diastolic blood pressure).

Diastolic blood pressure (mm of Hg)	TA group	EACA group	p
	Mean ± SD	Mean ± SD	
Baseline	74.40±6.69	73.73±6.70	0.701
Prebypass	67.00±3.00	66.26±5.11	0.501
Postbypass	63.40±2.78	64.26±1.77	0.156
1 hr	65.26±3.30	64.96±3.92	0.750
2 hr	66.46±4.05	66.83±7.45	0.814
3 hr	65.40±3.48	65.50±4.55	0.924
4 hr	66.06±3.25	65.26±3.21	0.342
5 hr	74.56±8.26	74.60±9.64	0.989
6 hr	66.23±2.40	66.00±3.56	0.767
9 hr	64.00±2.57	65.13±3.87	0.187
12 hr	66.86±3.81	66.13±3.01	0.412
18 hr	66.43±2.87	66.23±3.19	0.800
24 hr	66.93±3.88	66.16±2.66	0.377

The diastolic blood pressure is recorded at hourly interval up to first 6 hour thereafter at 9, 12, 18 and 24 hours. Mean diastolic blood pressure at specified interval in each group is shown in table no 12. Mean diastolic blood pressure did not vary significantly between two groups showing hemodynamic stability.

Central venous pressure

Table 12. Comparison of TA versus EACA (central venous pressure).

CVP	TA group	EACA group	p
	Mean ± SD	Mean ± SD	
Baseline	6.06±0.73	6.26±0.63	0.284
Prebypass	6.36±0.49	6.43±0.56	0.628
Postbypass	6.46±0.50	6.33±0.60	0.360
1 hr	4.90±1.24	5.53±1.38	0.067
2 hr	4.70±1.44	4.33±1.60	0.356
3 hr	5.63±1.06	5.53±0.89	0.696

CVP	TA group	EACA group	p
	Mean ± SD	Mean ± SD	
4 hr	5.46±0.50	5.60±1.22	0.583
5 hr	6.56±0.50	6.30±0.74	0.111
6 hr	6.50±0.50	6.46±0.50	0.800
9 hr	6.83±1.08	6.56±0.50	0.227
12 hr	6.23±0.50	6.40±0.72	0.305
18 hr	6.60±0.83	6.40±0.56	0.273
24 hr	6.26±0.58	5.86±1.07	0.078

The central venous pressure is recorded at hourly interval up to first 6 hour thereafter at 9, 12, 18 and 24 hours. Mean central venous pressure at specified interval in each group is shown in table no 13. Mean central venous pressure did not vary significantly between two groups. Mean central venous pressure was slightly lower in early postoperative period.

Hemoglobin %

Table 13. Comparison of TA versus EACA (Hb %).

Hb %	TA group	EACA group	p
	Mean ± SD	Mean ± SD	
Baseline	11.66±1.41	11.43±0.99	0.464
Prebypass	11.16±1.36	11.16±1.57	1.00
Postbypass	10.80±1.21	10.46±1.27	0.599
1 hr	9.45±1.08	9.30±1.20	0.387
2 hr	8.73±1.43	8.36±0.93	0.245
3 hr	9.10±1.26	8.97±1.02	0.672
4 hr	9.46±1.25	9.18±1.37	0.407
5 hr	9.45±1.24	9.23±0.93	0.442
6 hr	9.83±1.39	9.54±0.73	0.317
9 hr	9.90±0.81	9.86±0.77	0.847
12 hr	9.87±1.08	9.83±0.79	0.871
18 hr	9.74±1.18	9.76±0.62	0.913
24 hr	10.63±1.29	9.80±0.48	0.002

The Hb% is recorded at hourly interval up to first 6 hour thereafter at 9, 12, 18 and 24 hours. Mean Hb% at specified interval in each group is shown in table no 14. Mean Hb% was slightly higher in TA group as compared to EACA group. The difference was not statistically significant up to 18 hours. But the difference became statistically significant at 24 hours.

Urine output

Table 14. Comparison of TA versus EACA (urine output).

Urine output (ml)	TA group	EACA group	p
	Mean ± SD	Mean ± SD	
Baseline	71±13.22	66±19.49	0.337
Prebypass	107±12.63	110±13.51	0.328
Onbypass	151±24.54	142.76±51.72	0.434
Postbypass	106.33±15.42	106.33±17.90	1.000
1 hr	102.66±13.11	97.66±11.94	0.128
2 hr	100.66±20.16	106.66±13.97	0.186
3 hr	98.66±18.70	106.33±13.97	0.090
4 hr	108.33±28.41	105±14.32	0.568
5 hr	107.33±13.37	103.66±11.88	0.266
6 hr	117.66±14.06	117.66±12.78	1.000
9 hr	392.66±28.87	390.66±56.86	0.864
12 hr	371.33±45.76	362.66±39.64	0.436
18 hr	621±72.21	623.66±124.44	0.920
24 hr	1279.33±204.78	1254.33±60.90	0.728

Urine output was recorded at hourly interval up to first 6

hour thereafter at 9, 12, 18 and 24 hours. Mean urine output at specified interval in each group is shown in table no 12. Mean urine output did not vary significantly between two groups showing that both groups were comparable in terms of urine output.

Platelet count

Table 15. Comparison of TA versus EACA (platelet count).

Platelet count (in thousands)	TA group	EACA group	P
	Mean ± SD	Mean ± SD	
Baseline	318.86±66.85	291.96±46.95	0.77
Prebypass	238.66±54.42	227.76±47.06	0.410
Postbypass	210±35.15	201±71.86	0.552
1 hr	241.46±68.09	217±72.43	0.189
2 hr	227.13±76.83	260.70±55.59	0.057
3 hr	294.96±67.51	296.63±55.52	0.917
4 hr	258.46±39.26	250.70±55.59	0.534
5 hr	251.86±67.09	245.70±55.59	0.700
6 hr	252.63±68.72	250.70±55.59	0.905
9 hr	252.13±61.46	246.63±55.52	0.717
12 hr	251.06±57.72	243.36±72.43	0.651
18 hr	255.86±67.09	245.36±72.43	0.563
24 hr	266.46±39.26	243.63±55.52	0.071

Platelet count was recorded at hourly interval up to first 6 hour thereafter at 9, 12, 18 and 24 hours. Mean platelet count at specified interval in each group is shown in table no 12. Mean platelet count did not vary significantly between two groups showing that both groups were comparable in terms of platelet count.

4. Discussion

One of the common problems encountered in cardiac surgery and extracorporeal circulation is excessive bleeding. This bleeding contributes to both morbidity and mortality complicate postoperative care, resulting in transfusion of blood and blood products that are expensive and also carries the risk of infection to the recipient. Because both bleeding itself and the transfusions administered to compensate for blood loss have an untoward impact on outcomes, there is strong motivation to decrease the occurrence of bleeding associated with cardiac surgical procedures in the first place. The armamentarium to control bleeding includes careful surgical dissection, meticulous haemostasis and pharmacological management with new generation antifibrinolytic agents. From nanotechnology, there is only one step to nanomedicine, which may be defined as the monitoring, repair, construction, and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures [7].

Since Platelet dysfunction and fibrinolysis can contribute to bleeding after open heart surgery, the administration of antifibrinolytic agents appears to be a suitable approach to reducing postoperative bleeding in patient with open heart surgery. Inexpensive antifibrinolytic agents like Epsilon amino caproic acid and tranexamic acid have been shown to

reduce blood loss associated with many surgeries. Epsilon amino caproic acid and tranexamic acid primarily exert their antifibrinolytic effect by forming a reversible complex with plasminogen, which inhibits its conversion to plasmin and it's binding to fibrin. Therefore, it is not surprising that D-dimers were reduced in patients exposed to epsilon amino caproic acid and tranexamic acid, especially since the concentration of D-dimers is a sensitive measure of fibrinolysis. Since plasmin activates platelets, antifibrinolytic may also affect hemostasis by preventing plasmin induced platelet activation [8].

As efficacy of antifibrinolytic agents to decrease the postoperative bleeding has been well documented in literature so it would have been unethical to conduct placebo control trial. Therefore we decided to compare the efficacy of lysine analogue EACA and tranexamic acid in reducing postoperative blood loss and transfusion requirement following mitral valve replacement surgery.

As estimates of intraoperative blood loss are too inaccurate for study purpose, so we collected and measured total chest tube drainage at specified interval up to 24 hrs as per study protocol, starting from the time of chest closure.

Harrow et al in their dose response study of tranexamic acid found that lowest dose was 10 mg/kg followed by 1 mg/kg/hr. However, the lowest median mediastinal drainage in their study was with a dose 20 mg/kg followed by 2 mg/kg/hr [9] and same was in Shore-Lesserson et al [10]. The same dose of tranexamic acid was chosen for the current study. Dose of EACA is based on Dowd et al study to maintain blood EACA concentrations at or above 260 mg/L [11]. These studies showed the heterogeneity of sample population selected for their studies, to avoid this we selected uniform sample population i.e. patients undergoing only mitral valve replacement surgery.

In our study we decided to administer EACA or tranexamic acid immediately after induction of anaesthesia and prior to skin incision to reduce the total amount of blood in the postoperative period. Prior studies have noted that once significant bleeding had developed, the usefulness of antifibrinolytic administration were unpredictable. This is not unexpected, since the breakdown of fibrin results in release of fibrinopeptides that interfere with the polymerization of fibrin, hereby functioning as an anticoagulant. The unique feature in this study is that the antifibrinolytics are extended for 6 hour in post operative period. Due to the fact that hemodynamic instability, chances of post operative bleeding and incidence of re exploration are more frequent in first few hours after surgery.

The important finding of this study is that tranexamic acid significantly reduces postoperative bleeding when compared to EACA in patients undergoing mitral valve replacement surgery. In our study we found that mean blood loss in 24 hours with tranexamic acid is 416 ± 47.74 (ml) which is lower than epsilon amino caproic acid 489 ± 42.12 (ml). This difference is statistically significant. The mean blood loss in tranexamic acid was statistically significant lower than EACA in first 6 hours (Table no 4, 5). Henry *et al.* (2007) in

a similar study reported insignificant difference between tranexamic acid and EACA. They found that there was no statistically significant difference between TA and EACA in the volume of blood lost during the post-operative period. But the population under consideration in this study was not uniform. Pattern of bleeding in CABG, congenital defect repair, redo surgery, and valve replacement surgery is different. Dose regimen used in study was different. We had a uniform sample i.e. patients undergoing mitral valve replacement surgery and we extended duration of drug infusion up to first 6 hour in post operative period which is much versatile period.

Our findings are consistent with Pinolsky et al and Casati et al as they found that tranexamic acid and EACA effectively inhibited fibrinolytic activity intraoperatively and throughout the first 24 hours postoperatively, but again the populations under consideration in these studies were not uniform. Tranexamic acid was more effective in reducing blood loss postoperatively in paediatric patients undergoing cardiac surgery.

5. Limitation of Our Study

We selected the dose of TA from study of Shore-lesserson to provide necessary therapeutic concentration and similarly dose of EACA is based on study of Butterwoth et al to provide constant therapeutic level of 260ng/ml. We could not measure the plasma level of drugs in our study. We could extend this study with increased and decreased doses to compare results. To generalize the result we need to conduct multi centric trial with large sample size. Ideally FFP should be administered according to coagulation profile and INR. But in our study FFP were transfused as per anesthesiologists /surgeons view or in the presence of massive blood transfusion.

6. Conclusion

Tranexamic acid is more efficacious than ϵ amino caproic acid in regard to decrease postoperative blood loss and blood product requirement. Who were undergoing mitral valve replacement surgery treated with tranexamic acid had 73ml less total blood loss in 24 hours, 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 mitral valve replacement surgery.

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