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Comparison of epsilon aminocaproic acid and tranexamic acid to control postoperative bleeding in patients undergoing mitral valve replacement surgery- A randomised double blind trial

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Introduction

In cardiac surgery, postoperative bleeding is associated with an increased incidence of surgical re-exploration, increased use of blood and blood products, significant morbidity such as renal failure, sepsis, arrhythmias,etc. and increased mortality.(1)

Pharmacological therapy to reduce bleeding in the postoperative period of CPB had been studied since the report by Mammem et al(2) with Aprotinin in 1968. At present, three antifibrinolytic agents—two synthetic [Epsilon amino caproic acid (EACA), Tranexamic acid (TA)] and one natural (Aprotinin)—are available for clinical use. Aprotinin has shown its effectiveness in reducing postoperative hemorrhage in more than 40 randomized clinical trials and 2 meta-analyses.(3,4) In addition, there are concerns about potential thrombosis-related side effects and allergic reactions with antifibrinolytic agents. For these reasons, prophylactic use of Aprotinin was often limited to patients at high risk for bleeding (e.g. reoperations) or those for whom transfusions were not acceptable because of religious beliefs (e.g. Jehovah's Witnesses).(5) Epsilon amino caproic acid and Tranexamic acid are antifibrinolytic agents that do not have the increased risk of anaphylaxis upon re-exposure. Treatment with either EACA/Tranexamic acid (TA) prior to CPB had been shown to reduce blood loss in perioperative period.(5,6) Many trials were conducted to compare EACA or TA with placebo, but very few studies (done by Pinolsky et al,(7) Maineri et al,(8) and Hardy JF et al(9)) were conducted for comparison of EACA and TA in cardiac surgery. So this study was done using Tranexamic acid to compare against Epsilon amino caproic acid. Also, a placebo control group was not used for this study since the efficacy of the antifibrinolytic drugs has been established in the literature. So it would have been unethical to conduct placebo control study. Aim and objective of the study were mentioned below:

Aim

To compare the Epsilon amino caproic acid and Tranexamic acid to control postoperative bleeding in patients undergoing mitral valve replacement surgery.

Objectives

To compare in both groups:-

1. Postoperative blood loss in first 24 hour,
2. Number of units of blood, blood component transfused in first 24 hour post operatively,
3. Hb % on day 2,
4. INR (International Normalised Ratio) on day 2,
5. Re-exploration rate to find out cause of bleeding

Materials and Methods

The present study was randomised controlled double blind trial carried out in department of Anaesthesiology (CVTS OT), at a government tertiary care hospital. Approval for the study was taken from the institutional ethics committee. Present study was carried out from January 2009 to November 2010. Study population was selected from patients undergoing mitral valve replacement surgery. Inclusion and exclusion criteria for selection of study subjects were as follows:

Inclusion Criteria:

1. Patients posted for elective mitral valve replacement surgery.
2. Age from 18-60 years, Patients of both sex were included
3. Preoperative Haemoglobin >10 gm%
4. Hematocrit >30%
5. Normal coagulation profile including PT (Prothrombin Time), INR

Exclusion Criteria:

1. History of (H/O) bleeding diathesis or urinary tract bleeding
2. Allergic reaction to anti fibrinolytic drug
3. Emergency operation
4. Preoperative renal failure (serum creatinine >2)
5. Deranged coagulation profile Prothrombin Index (PI) <75% or INR>2
6. H/O thrombosis
7. Pregnancy
8. Patient on ant platelet treatment within 7 days of surgery
9. Redo surgery

10. Patient's refusal

Sample size calculation: Sample size calculation was done based on finding in pilot study carried out among 10 patients in each group. In pilot study blood loss (ml) in group 1, receiving Tranexamic acid was 407.12 ± 54.16 ml & in group 2 receiving EACA was 478.43 ± 55.29 ml. By using formula for sample size estimation for randomized controlled trial with uniform allocation, sample size came out to be 26. Considering dropout rate of 10 %, we decided to take 30 patients in each group.

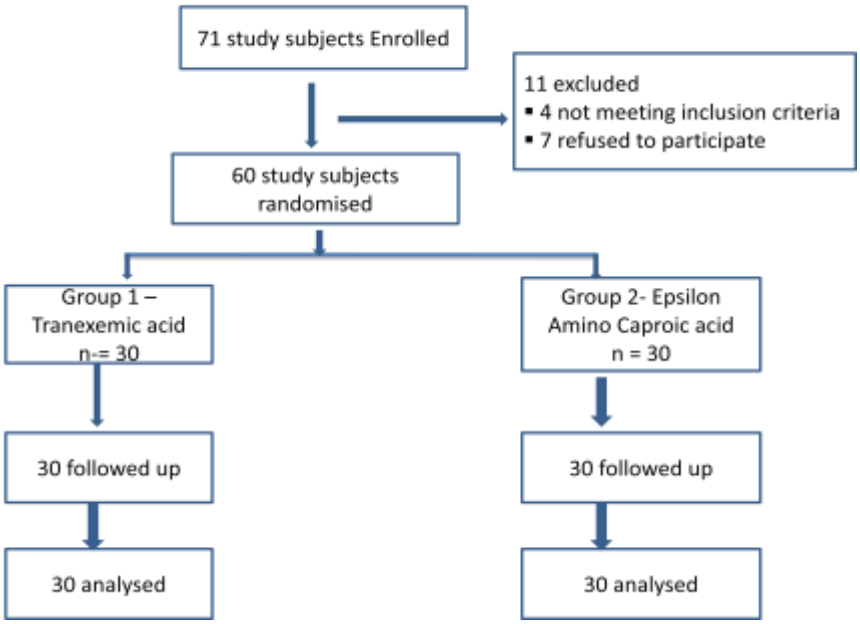
Intervention: Total; 71 subjects were enrolled, 11 subjects were excluded from the study and 60 patients were randomly assigned in a prospective, double blind fashion to one of the two groups (Chart 1). Randomization was done with block randomization method using 5 blocks of size 6.

Group 1: **Tranexamic Acid** (TA n=3O**)** 20 mg/kg body weight diluted to 20 cc with normal saline was given over 20 min as bolus at time of induction of anaesthesia, & infusion of 2 mg/kg/hr started was continued throughout surgery till 6 hours post operatively in recovery room.

Group 2: **Epsilon Amino Caproic Acid** (EACA n=30**)** 100 mg/kg body weight bolus slowly was given over 20 min as bolus at time of induction of anaesthesia, & infusion 20 mg/kg/hr started was continued throughout surgery till 6 hours post operatively in recovery room.

Same brands of study drugs were used throughout study period which were made available through hospital supply.

Chart 1: Trial Profile



Methodology

Preoperative written informed consent was obtained from study subjects before inclusion in study. A detailed pre anaesthetic evaluation was carried out for each patient. All patients were investigated as per hospital protocol. Baseline vitals like Heart Rate (HR) & Rhythm, SPO2, Respiratory rate were monitored before induction. Sedation with I.V. Fentanyl 3 g/kg and Midazolam 0.05 mg/kg was administered. Central venous, Radial Arterial & Femoral arterial line were established under local anaesthesia & invasive blood pressure as well as central venous pressure (CVP) was monitored.

Study drugs were given in sealed and coded envelopes as above mentioned protocol and administered by an anesthetist who was blinded for study.

Patient was induced with Inj. Thiopental 5-7mg/kg. Neuromuscular blockade was achieved and maintained with Vecuronium 0.15mg/kg. Intubation was done with the appropriate sized cuffed endotracheal tube. Anaesthesia was maintained on O_2, air & inhalational anaesthetic agent (1%-2% Sevoflurane or 0.6% -1.2% Isoflurane according to vital parameter) on semi closed circle system with CO_2 absorber and flow rate of 4 lit/min.

Bolus of Fentanyl, Midazolam, and Vecuronium were administered as per needs. (Mixture of Vecuronium 20 mg, Midazolam 10 mg, Fentanyl 500 mg mixture diluted to 50 cc started as infusion).

Heparin was given at a dose of 400 U/kg and supplemented as necessary to maintain Activated clotting time (ACT) > 460 sec while on Cardiopulmonary Bypass.

CPB was maintained with roller pump utilizing a membrane oxygenator. All patients underwent standard non pulsatile normothermic or mildly hypothermic (28º C to 32º C) Cardiopulmonary 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.

Heparin was neutralized with Protamine 1.5 mg/100 U. Inotropes, Vasopressors, Vasodilators etc were administered as per needs.

ACT was performed at the following time intervals:

- Baseline
- After Heparin administration
- After Protamine titration
- Post operatively if bleeding is more than 200 ml/hour

Postoperative blood loss in form of chest tube drain was recorded every hourly till 6 hours, and then at 9, 12 18 & 24 hour, number of units of whole blood, blood component (FFP, Platelet) transfused post operatively in recovery room in 24 hrs, number of patients re-explored in 24 hour, Hb % 24 hour post operatively, Coagulation profile in form of INR 24 hours after surgery were recorded. Patient was monitored for renal function in form of urine output, kidney function test on next day and also for thrombotic complications like stroke (level of consciousness, convulsion, sensory or motor loss), ECG changes of acute myocardial infarction. We followed standard hospital protocol for transfusion and re-exploration uniformly.

Final Statistical Analysis: The primary analysis was an intent-to-treat analysis. Patients were analyzed in the group to which they had been randomly assigned. Descriptive analysis included mean, standard deviation, and percentages. For inferential statistics, continuous parameters were compared between Group I and Group II by performing unpaired t-test. Mann Whitney U test was used for non normalized data. p value less than 0.05 was considered as statistical significance. Data analysis was performed using MS- Excel and Open Epi software.

Results

Baseline characteristics of the study subjects were comparable in both groups (Table 1). Fig. 1 show baseline characteristics of both groups graphically. Data of preoperative parameters had been shown in Table 2. There were no statistically significant preoperative intergroup differences with respect to Hb%, INR & kidney function test.

Table 1: Preoperative Baseline characteristics in both groups

Variable	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
Weight (kg)	42.9 ± 12.5	43.5 ± 6.89	0.8161
Height (cms)	153 ± 12.70	155.86 ± 11.05	0.355
Body mass index (kg/m^2)	18.00 ± 3.49	17.98 ± 1.90	0.978

*t test

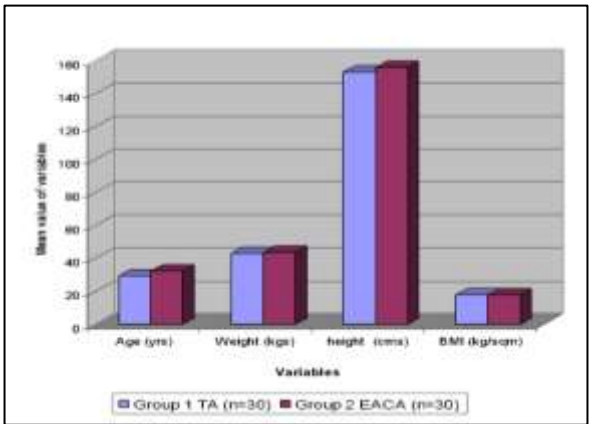


Fig. 1: Preoperative demographic profile of patients in both study groups

Table 2: Preoperative investigations in both groups

Variable	Group 1 (TA n=30) Mean ± SD	Group 2 (EACA n=30) Mean ± SD	p*
Hb %(g/dl)	11.6 ± 1.4	11.4 ± 1.01	0.44
INR	1.14 ± 0.21	1.13 ± 0.11	0.835

*t test

Mean duration of bypass in TA group was 72.74 ± 27.07 minutes and that in EACA group was 71.78 ± 32.26 min. which was comparable and no significant difference was found. No significant difference between ACT was observed in two groups (Table 3).

Table 3: Intraoperative coagulation status and duration of cardiopulmonary bypass in both groups

Parameter	Group1 (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 Protamine (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

*t test

Postoperative blood loss was measured in terms of amount of blood collected in chest drain at 24 hours in both groups. Fig. 2 shows the graphical postoperative blood loss trends in both groups. The mean blood loss was higher in EACA group postoperatively as compared to TA group up to first 6 hrs. Statistically this difference was significant. After 6 hours though mean blood loss was higher in EACA group as compared to TA but the difference was not statistically significant.

Total blood loss after 24 hours in EACA group i.e. 489 ± 42.12 ml was significantly higher as compared to 416.00 ± 47.74 ml in TA group. In TA group 19 out of 30 patients i.e. 63.33 % patients received transfusion whereas in EACA group 26 out of 30 patients i.e. 86.67% received transfusion (Fig. 3).

Number of units of whole blood and blood components transfused in both group was shown in Table 4. Significantly higher units of whole blood transfusion were required in EACA group. Number of units of platelets and FFP required per patient did not vary significantly among both groups. (Fig. 4)

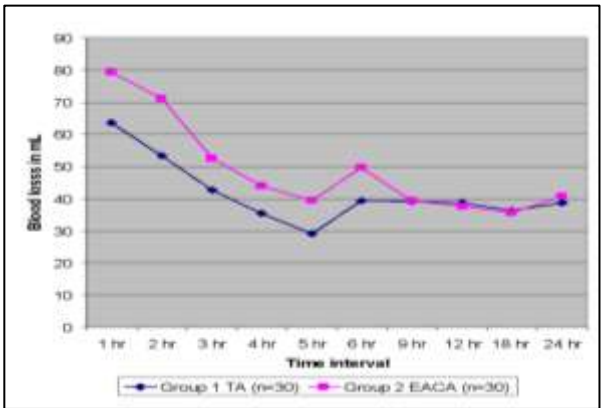


Fig. 2: Post-operative blood loss trends in both groups

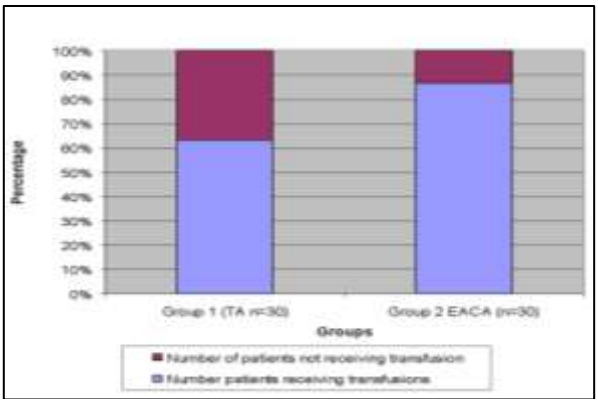


Fig. 3: Percentage of patients receiving transfusion

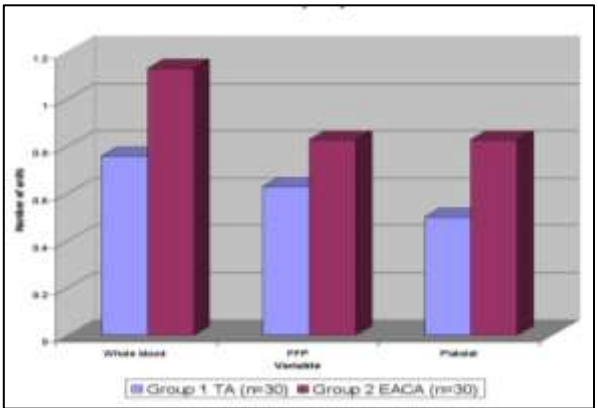


Fig. 4: Units of blood and blood components transfused per patient

Table 4: Units of blood, blood components transfused in both groups

Total transfusion (in Units)	Group 1 (TA n=30)	Group 2 (EACA n=30)	p (Mann Whitney U test)
	Median (interpercentile range 25th -75th)	Median (interpercentile range 25th -75th)	
Whole Blood (units)	1(0-1)	1(1-2)	0.034*
FFP (units)	0(0-1)	1(0-1)	0.229
Platelet (units)	0(0-1)	1(0-2)	0.103

*Significant

Hb% and INR was measured on day 2 at 24 hrs. Mean Hb% and Mean INR in both groups were shown in table 5. It was observed that mean Hb% of patients in TA group (10.74±1.23) was significantly better as compared to that of patients in EACA group (9.95 ± 1.26) on second day. Also it was observed that mean INR on day 2 in group 1 of TA was 1.41 ± 0.26 & in group 2 it was 1.33 ±0.28. The difference was not statistically significant.

None of the patient in both groups required re-exploration. No complications like kidney failure, stroke, AMI were observed in either group. Only 1 patient in EACA group had convulsions.

Table 5: Mean Hb% & mean INR on second day

Variable 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

t test, * Significant

Discussion

Tranexamic acid had been used in wide range of doses. Harrow et al[10] in their dose response study of Tranexamic acid found the lowest median mediastinal drainage in their study was with a dose 20 mg/kg followed by 2 mg/kg/hr. So the same dose of Tranexamic acid was chosen for present study. Same dose had also been used by Shore-Lesserson et al.[11] Similarly, dose of EACA was based on Butterworth et al[12] study so as to maintain blood EACA concentration at or above 260 mg/L.

In the present study we administered EACA or Tranexamic acid immediately after induction of anaesthesia and prior to skin incision to reduce the total amount of blood loss in the postoperative period were extended for 6 hour in post-operative period. Prior studies had noted that once significant bleeding had developed, the usefulness of anti-fibrinolytic administration were unpredictable.[13] Due to the fact that hemodynamic instability, chances of postoperative bleeding & incidence of re-exploration were more frequent in first few hours after surgery, so the investigation was concentrated in the initial six postoperative hours, from when, in general, stabilization in the drainage occurs.

The important finding of the present study was Tranexamic acid significantly reduced postoperative bleeding when compared to Epsilon amino caproic acid in patients undergoing mitral valve replacement surgery.

Findings in present study were consistent with that studied by Pinolsky et al,[7] Maineri et al,[8] and Hardy JF et al.[9] Pinolsky et al[7] found that, Tranexamic acid and EACA effectively inhibited fibrinolytic activity intraoperatively and throughout the first 24 hours postoperatively. Tranexamic acid was more effective in reducing blood loss postoperatively following CABG. However pattern of bleeding as studied by Hardy JF et al[9] in primary myocardial revascularization was different than observed in our study done in mitral valve replacement surgery. Secondly dose pattern in their study and in present study was different.

Brown et al[14] found that EACA and Tranexamic acid did not differ significantly in the amount of total blood loss. A similar non-significant difference was reported by Henry et al (2007).[15] They found that there was no statistically significant difference between Tranexamic acid and Epsilon amino caproic acid in the volume of blood lost during the postoperative period. But the population under consideration in these studies were not uniform, pattern of bleeding in CABG, congenital effect repair, redo surgery, valve replacement surgery was different. Dose regimens used in studies were different than our study. Also, we had extended duration of drug infusion up to first 6 hour in postoperative period which was much versatile period.

In this study 63.33% patients in TA group received transfusion whereas in EACA group 86.67% patients received transfusion. The finding in present study showed that Tranexamic acid group required less whole blood transfusion as compared to EACA. This was supported by findings of Hardy JF et al[9] and Armellin et al.[16] They showed reduction in usage of red blood cells and fresh frozen plasma and the proportion of patients receiving blood products in Tranexamic acid group was less as compared to placebo.

Meta-analyses done by Laupacis A et al[3] showed that Tranexamic acid as compared to placebo had reduced the proportion of patients receiving allergenic blood transfusions (OR 0.50, 95% CI: 0.34–0.76, 12 trials, 882 patients). In the second meta-analysis, Levi et al[4] showed that lysine analogues (TA and EACA) decreased perioperative blood loss and need for transfusion. The likelihood of receiving a transfusion was found to be lower for patients treated with lysine analogues compared to those treated with placebo (OR 0.46, 95% CI: 0.34–0.64, 14 studies, 801 patients). However, these studies did not report the effects of these drugs in uncomplicated cardiac surgery alone and did not differentiate the effects of Tranexamic acid and Epsilon aminocaproic acid separately. We did not found statistically significant difference between two groups in regard to platelet and FFP transfusion in our study. This was consistent with study by Goncalves FD et al.[6] who revealed significant decreased requirement for the volume of RBC concentrates in valve disease patients receiving Tranexamic acid as compared to placebo but the difference was not significant for FFP and platelet transfusion.

In present study, patients in Tranexamic acid group had better mean Hb% on next day, as compared to Epsilon aminocaproic acid group. This might be due to less postoperative bleeding in Tranexamic acid group. This could be explained on the basis of greater potency and longer duration of action of Tranexamic acid. This finding was consistent with that observed by Katsaros D et al.[17] They found that the hemoglobin concentration at discharge was significantly greater in the Tranexamic acid group than in the control group.

None of the patient in either group underwent re-exploration. Meta-analysis by Levi et al[4] showed that need for re-exploration for any reason within 72 hours of the operation was also decreased in patients treated with lysine analogues (OR 0.44, 95% CI: 0.22–0.99, 11 studies, 1026 patients).

In conclusion, this was randomised double blind trial carried out for the comparison of Epsilon Amino Caproic Acid and Tranexamic acid to control postoperative bleeding in patients undergoing mitral valve replacement surgery. Tranexamic is more efficacious than Epsilon amino caproic acid in regard to decrease in postoperative blood loss and decrease in

blood requirement in patients undergoing mitral valve replacement surgery. Also in patients receiving tranexamic acid mean Hb on day 2 was significantly better than those receiving EACA.

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