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Research Article

A Comparitive Study Between Tranexamic Acid And Epsilon-Amino-Caproic Acid (EACA) In Reducing Post-Operative Bleeding In Patients Undergoing on Pump Coronary Artery Bypass Grafting (CABG) Surgeries

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Abstract: ***Background:*** The amount of strain that cardiac surgery exerts on blood bank services is an example that emphasises the need for multimodal blood conservation strategy. The most common factor which is being attributable to increase bleeding after cardiac surgery is hyperfibrinolysis. Thererfore the use of antifibrinolytics during high risk cardiac surgery becomes inevitable. Commonly used antifibrinolytic include Tranexamic Acid(TA) and Epsilon-amino-caproic acid **(**EACA) .The aim of our study was to compare the effectiveness of both TA and EACA in reducing post-surgical bleeding in on-pump CABG surgeries and to assess the post-operative complications associated with its use.Material and Methods: After obtaining informed written consent, approval of ethics and research committee patients who were scheduled for on-pump CABG were included in the study. Patients were divided into two groups randomly by using a comupter generated randomized block design namely group TA(n=40) and group EACA (n=40). TA group received tranaxamic acid at a dose of 10mg/kg IV over 20 min at the time of induction then 1-2 mg/kg in CPB prime followed by 1 mg /kg/hr infusion during surgery. Group EACA received EACA in a dose of 100mg/kg/IV over 20 min at the time of induction then 5-10mg/kg in CPB prime followed by 10mg/kg/hr. infusion during surgery. Patients were assessed for blood loss and were monitored for fibrinogen level and D- dimer levels. Other parameters which were assessed included Re-exploration and post-operative complications. ***Result:*** Primary outcomes like bleeding at 4hrs, there was no significant difference between the groups but when total bleeding at 24hrs. was compared there was a significantly lesser bleed in group TA group compared to group EACA (P=0.0022).The requirement of PRBC in group TA was for 3 patients, where as in EACA group 4 patients required PRBC (P>0.05).There was no significant difference in the rate of post-operative complications between the groups.(P>0.05) .Conclusion : Our study showed that TA is more effective when compared to EACA in inhibiting fibrinolysis during on pump CABG surgery and thus results in decreased post-operative bleeding. Our study also re-emphasized the fact that neither of the drug led to any additional risk of post-operative thrombotic complications.

Keywords: TA : Tranexamic Acid, EACA : Epsilon-amino-caproic acid , CPB: Cardio Pulmonary Bypass, PRBC: Packed Red Blood Cell,FFP: Fresh Frozen Plasma.

INTRODUCTION

For decades the most common indication for blood transfusion is perioperative bleeding and cardiac surgery ranks high on the list. The reason which is being attributable to this complication is the institution of Cardio Pulmonary Bypass (CPB). CPB leads to series of events like compliment activation, platelet Activation and increased fibrinolysis which contributes to increase post-operative bleeding (Paparella, D. *et al.*, 2006). Post-operative bleeding in itself carries a high risk for in hospital mortality. Cardiac surgical pateints who are taken up for re explorartion due to bleeding carry a fourfold increase in mortality and sternal wound infection (Bridges, C. R. 2007). Therfore a multimodal approach is recommended to reduce perioperative bleeding which includes the use of anti fibrinolytic agents.

Anti fibrinolytic agents have been used during cardiac surgery to reduce the risk of post-operative bleeding. Most commonly used antifibrinolytic agents

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include Aprotinin and lysine analogs (Tranexamic acid TA and E- amino caproic acid EACA).

Aprotinin is a serine protease inhibitor which inhibits multiple proteases like plasmin, kallikrein, trypsin, and activated factor XII, thereby reducing blood loss. In 2007 a prospective study on high risk pateints undergoing cardiac surgery know as Blood conservation using Antifibrinolytics in a Randomized Trial (BART) reported an increased mortality with use of aprotonin compared to lysine analogs (Fergusson, D. A. *et al.,* 2008) . Later due to warning from Food and Drug administration (FDA) ,Bayer health care withdrew apportioning from the market. Now the Society of Thoracic Surgeons (STS) guidelines (Ferraris, V. A. *et al.,* 2011) recommend the use of anti-fibrinolytic agents (only lysine analogues), as a strategy to reduce perioperative blood loss during cardiac surgery.

Tranexemic acid (TA) is a synthetic antifibrinolytic that blocks lysine binding site on plasminogen molecule, thus inhibiting the interaction with plasmin and fibrin which leads to decreased post-operative bleeding (Mehr-Aein, A. *et al.,* 2007; & Greilich, P. E. *et al.,* 2009). Similarly EACA is a synthetic lysin analog which reduces the rate of plasmin formation and further decreases the degradation of fibrin to fibrin degradation product (FDP) (Sterns, L. P. 1967). Apart from this EACA also has a platelet sparing action which leads in inhibition of plasmin mediated platelet injury (Slaughter, T. F. *et al.,* 1997) .

Both TA and EACA have been shown to decrease post-operative bleeding associated with CPB.However there are no large studies comparing the effectiveness of both drugs in patients undergoing on pump CABG surgeries.

The aim of our study was to compare the effectiveness of both TA and EACA in reducing post-surgical bleeding in on-pump CABG surgeries with regards to the amount of blood loss at 4 hrs and 24 hrs as the primary outcome. The secondary outcome of our study included the rate of transfusion of packed red blood cell (PRBC), fresh frozen plasma(FFP) and platelets. Other parameters which were assessed included re exploration rates and post-operative complications.

MATERIAL AND METHODS

After obtaining informed written consent, approval of ethics and research committee patients who were scheduled for on-pump CABG were included in the study. This study was carried out between June 2019 to Feb 2020 at a tertiary care teaching hospital. Patients with concomitant valvular heart disease, recent Myocardiac Infarction (MI<4wks) Ejection Fraction <40%, Pre-existing neurological, pulmonary or hepatic dysfunction were excluded from the study.

Patients were divided into two groups randomly by using a computer generated randomized block design namely group TA(n=40) and group EACA (n=40). In both the group under strict aseptic precaution under local anaesthesia a wide bore peripheral IV cannula, right radial artery cannulation and right femoral artery cannulation was done for continuous hemodynamic monitoring. Anesthesia was induced with Inj etomidate (0.2mg/kg),Inj Fentanyl (3-5 ug/kg) and Inj Rocuronium (0.8-1mg /Kg). After induction of anesthesia right internal jugular vein cannulation was done with 7.5 Fr Triple lumen catheter and PA catheter was inserted. Anesthesia was maintained with air and oxygen (50%),sevoflurane (1-3%) and Inj Atracurium (0.5-1mg/Kg). After sternotomy and heparinization CPB was established once ACT was >420 Sec.

TA group received tranaxamic acid at a dose of 10mg/kg IV over 20 min at the time of induction then 1-2 mg/kg in CPB prime followed by 1 mg /kg/hr infusion during surgery. Group EACA received EACA in a dose of 100mg/kg/IV over 20 min at he time of induction then 5-10mg/kg in CPB prime followed by 10mg/kg/hr infusion during surgery . Later Inj Protamine was administered to reverse the effect of Heparin.

After completion of surgery patients were shifted to ICU and were assessed for blood loss at 4 hrs and 24 hrs . Indication for transfusion of PRBC was when haemoglobin levels were less than 8gm/dl. FFP was trasfused if post-operative drain was more than 250ml/hr in first hour. Platelet trasfusion was indicated if platelets counts were less than 50000/mm3. The degree of fibrinolysis was measured by Thromboelastography (TEG),(Hemostasis system,Haemoscope corporation USA)

Other parameters which were monitored included fibrinogen level and D- dimer levels at 4 hrs and 24 hrs. Re-exploration of case was considered if the bleeding was > 300ml/hr in first 2hrs. or if >200 ml/hr. for 4 consecutive hrs,with normal coagulation data.Patients were also observed for post-operative complications like MI,Stroke,Deep vein thrombosis (DVT),renal dysfunction and seizures for 72 hrs.

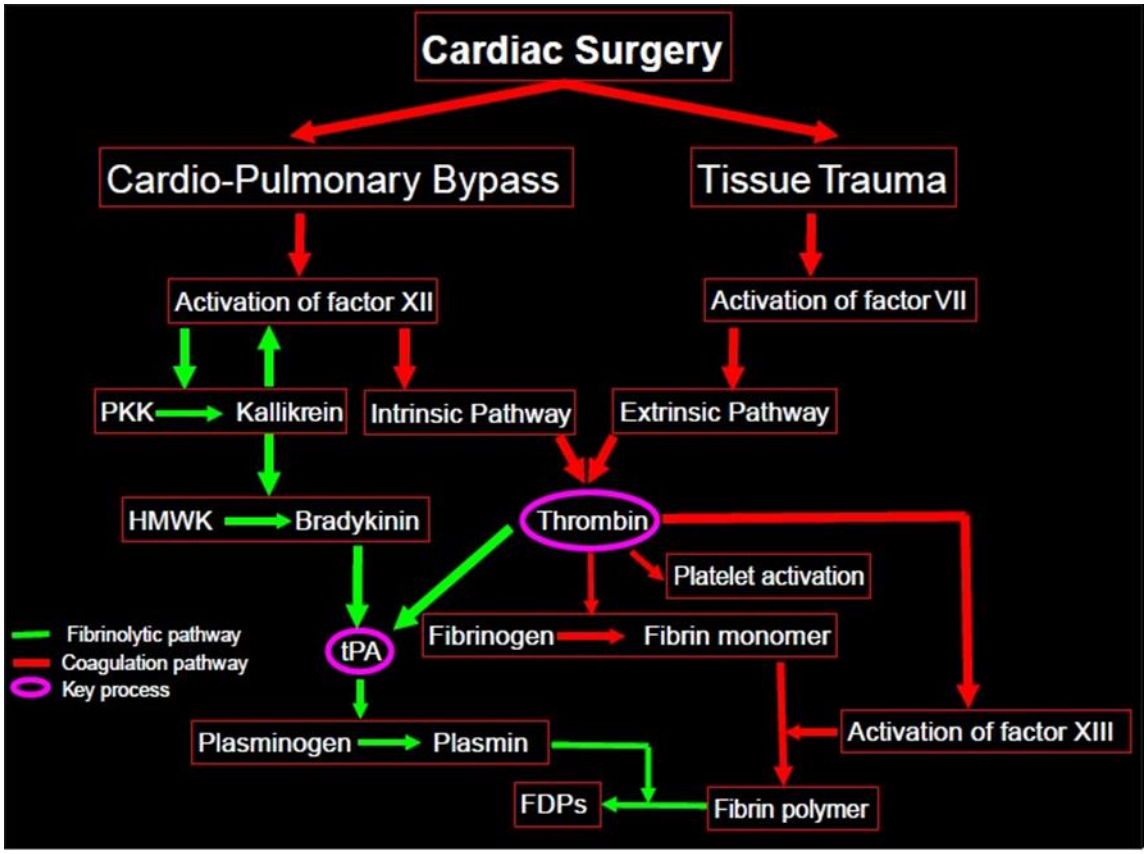

Figure 1: Flow diagram depicting activation of coagulation and fibrinolytic activities during cardiac surgery
PKK -Pre kallikrein; HMWK -High molecular weight kininogen; tPA -Tissue plasminogen activator; FDPs -Fibrin degradation products

Table 1. *Baseline Demography*

Parameter	Group TA (n=40)	Group EACA(n=40)	P
Age(Yrs)	68 ± 2	67 ± 3	0.967
Weight(Kg)	74 ± 3	76 ± 4	0.271
Height(Cm)	165 ± 3	162 ± 6	0.118
M/F(Gender)	26/14	28/12	0.739

TA= Tranexamic Acid EACA= Epsilon-amino-caproic-acid

Table 2. *Inra operative time and intrvention*

Variables	Group TA (n=40)	Group EACA(n=40)	P
Cross Clamp Time>50 min	10(25%)	10(25%)	1
CPB>70 min	14(35%)	15(37.5%)	0.793

Table 3. *Primary and secondary Outcome*

Parameter	Group TA(n=40)	Group EACA(n=40)	P
Bleeding at 4hrs(ml)	190(90-260)	210(110-320)	0.0321
Total Bleeding at 24 hrs(ml)	360(140-530)	440(170-740)	0.0022
PRBC Transfused	3	2	0.921
FFP Transfused	1	1	1
Platelet Transfused	1	1	1
Re Exploration	0	0	1

PRBC: Packed Red Blood Cell,FFP: Fresh Frozen Plasma

Table 4. *Post-operative Complications*

Parameters	Group TA (n=40)	Group EACA(n=40)	P
MI	0	1	0.981
Stroke	1	1	1
Seizure	1	0	0.981
PE	0	0	-
DVT	0	0	-
Doubling of S.Cr	0	1	0.981

MI: Myocardial Infarction DVT: Deep Vein Thrombosis PE: Pulmonary Embolism S. Cr: Serum Creatinine.

Statistical analysis was done with SPSS software version 19.0 normality of the test were checked using Kolmogorov-smirnov test. The values which were obtained were analyzed and were expressed as mean ± Standard Deviation (SD) and median ± range. For continuous variables for parametric data, Indepedent's test were used and for non-parametric data Mann-Whitney u test were used. For categorical data, Chi-Square test or fisher's exact test were used. A P Value of <0.05 was considered to be statistically significant.

RESULT

Demographic variables like age, weight, height, male-female ratio were comparable in both groups. (Table-1) The cross clamp time & duration on CPB were also comparable in both groups (Table-2). Primary outcomes like bleeding at 4hrs, there was no significant difference between the groups , group TA 190(90-260)ml versus group EACA210(110-320)ml (p =0.032) but when total bleeding at 24 hrs was compared there was a significantly lesser bleed in group TA 360(140-530)ml compared to group EACA 440(170-740)(P=0.0022).

The requirement of PRBC in group TA was for 3 patients, where as in EACA group 4 patients required PRBC (P>0.05). One patient in each group required FFP transfusion (P>0.05).Both the groups did not require any platelet transfusion & the transfusion rate was non-significant between the groups. Both the groups had no re exploration due to excessive bleeding.(Table-3).

There was no significant difference in the rate of post-operative complications between the groups.(P>0.05) (Table-4)

DISCUSSION

On pump CABG is associated with increased risk of post-operative bleeding compared to OPCAB (Wei, M. *et al.*, 2006; & Abu-Omar, Y., & Taggart, D. P. 2009) reason best attributable to use of CPB, which is associated with increased fibrinolysis & increased concentration of inflammatory mediators, which has urged researchers all around the world to investigate the probable role of anti fibrinolytics in on pump cardiac surgeries (Mariani, M. A. *et al.*, 1999).

In our study we found that there was no significant difference in the amount of post-operative bleeding at 4 hours between the groups however at 24 hrs there was a significant difference between both the groups with lesser bleeding in group TA compared to group EACA. This may be due to the fact the TA is 10 times more potent than EACA (Dhir, A. 2013). Similar findings were obtained in a study comparing TA & EACA with placebo conducted by Karski Karski, J. M. *et al.*, (1993).

Chauhan, S. *et al.*, (2004) & Falana, O., & Patel, G. (2014) while comparing both the drugs showed that there was no significant difference in the rate of post-operative transfusion of PRBC,FFP / Platelet or the rate of re-exploration for excessive bleeding,which was comparable with our study.

Post-operative blood transfusion after CABG is associated with increased long term mortality (Engoren, M. C. *et al.*, 2002).Therefore the role of these drugs in reducing the transfusion rate after on pump CABG is very significant. There were no difference in the rate of post-operative complication's between the group's. Hardy *Et al.*, in his study while comparing both the drugs did not find any significant difference between the drugs with regards to post-operative thrombo embolic complications (Hardy, J. F. *et al.*, 1998).

The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial (Myles, P. S. *et al.*, 2017) compared TA with placebo in patients undergoing coronary bypass surgery and demonstrated that patients who were randomly assigned to TA therapy had a significantly reduced risk for reoperations due to postoperative bleeding, as well as a decreased need for transfusion of any blood products. Based on these data, all the transfusion guidelines support the use

of antifibrinolytic agents in patients undergoing cardiac surgery with CPB (Ferraris, V. A. *et al.*, 2011).

There are controversies with regards to the dosing of the drug .A high dose (20mg/kg) TA is associated with increased risk of post-operative seizures and therefore a low dose (10mg/kg) regime is recommended (Manji, R. A. *et al.*, 2012). Armelin *et al.*, compared the low dose and high dose TA regiem and found no difference with respect to amount of post-operative blood loss or transfusion requirement (Armellin, G. *et al.*, 2004) In our study we used low dose TA dosing and did not find any significant post-operative complications.

CONCLUSION

Based on the results of our study it can be concluded that both TA & EACA effectively inhibits fibrinolysis during on pump CABG surgery and thus results in decreased post-operative bleeding.When compared between the two, TA was slightly better with respect to post-operative bleeding at 24hrs.

Fibrinolytic system plays an important role in maintaining the vascular patency and thus the vascular haemostasis . After institution of CPB there is extensive tissue injury and the equilibrium shifts leading to increased fibrinolysis which contributes to bleeding and coagulopathy. Therefore a comprehensive approach to blood conservation during cardiac surgery is highly recommended including use of antifibrinolytic agents.

The use of antifibrinolytic agents must be governed by an view of their inherent risks and benefits. Even after extensive research it is still very difficult to predict whether any given patient is at increased risk for bleeding or thrombosis. Antifibrinolytic therapy must be used when hyper fibrinolysis occurs and it seems attractive to have point-of-care fibrinolysis monitoring to guide the therapy. In an ideal world, it will also be nice to know the genetic variants for fibrinolysis or prothrombotic states, as some patients may not require any agent.

Our study also re-emphasized the fact that neither of the drug led to any additional risk of post-operative thrombotic complications & thus can potentially become an standard of care for blood conservation in patients undergoing on pump CABG.

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