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A Comparitive Study between Tranexamic Acid and Epsilon-Amino-Caproic Acid in Reducing Post-Operative Bleeding in Patients Undergoing on Pump CABG Surgeries

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Abstract

The amount of strain that cardiac surgery exerts on blood bank services is an example that emphasizes the need for multimodel blood conservation stratergy. The most common factor which is being attributable to increased 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 computer generated randomized block design namely group TA (n=40) and group EACA (n=40). TA group received tranaxamic acid at a dose of 10 mg/kg IV over 20 min at the time of induction then 1-2 mg/kg in CPB prime followed by 1 mg/kg/hour infusion during surgery. Group EACA received EACA in a dose of 100 mg/kg/IV over 20 min at the time of induction then 5-10 mg/kg in CPB prime followed by 10 mg/kg/hour infusion during surgery. Patients were assessed for blood loss and were monitored for fibrinogen level and D-dimer levels, Re-exploration and post-operative complications. Result Primary outcomes like bleeding at 4 hours, there was no significant difference between the groups but when total bleeding at 24 hours 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, whereas 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 from our study we concluded that both TA and 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 24 hours. Our study also re-emphasized the fact that neither of the drug led to any additional risk of post-operative thrombotic complications.

Keywords: Tranexamic acid; Epsilon-Amino-Caproic acid (EACA); Cardio Pulmonary Bypass (CPB); Packed Red Blood Cell (PRBC); Fresh Frozen Plasma (FFP)

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 increased post-operative bleeding [1]. Post-operative bleeding in itself carries a high risk for in hospital mortality. Cardiac surgical patients who are taken up for re exploration due to bleeding carry a fourfold increase in mortality and sternal wound infection [2]. Therefore a multimodal approach is recommended to reduce perioperative bleeding which includes the use of antifibrinolytic agents. Antifibrinolytic agents have been used during cardiac surgery to reduce the risk of post-operative bleeding. Most commonly used antifibrinolytic agents 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 [3]. Later due to warning from Food and Drug Administration (FDA), Bayer health care withdrew aprotinin from the market. Now the Society of Thoracic Surgeons (STS) guidelines [4] 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[5,6]. 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) [7]. Apart from this EACA also has a platelet sparing action which leads in inhibition of plasmin mediated platelet injury [8]. 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 hours and 24 hours 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, re exploration rates, post-operative D-dimer and fibrinogen levels.

Materials 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 February 2020. Patients with concomitant valvular heart disease, recent Myocardiac Infarction (MI<4 wks) Ejection Fraction<40%, Preexisting 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 anesthesia 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 (0.2 mg/kg), Inj Fentanyl (3-5 ug/kg) and Inj Rocuronium (0.8-1 mg/Kg). After induction of patient 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 (0.5-1 mg/Kg). After sternotomy and heparinization CPB was established once ACT was >420 Sec. TA group received tranaxamic acid at a dose of 10 mg/kg/IV over 20 min at the time of induction then 1-2 mg/kg in CPB prime followed by 1 mg/kg/hour infusion during surgery. Group EACA received EACA in a dose of 100 mg/kg/IV over 20 min at the time of induction then 5-10 mg/kg in CPB prime followed by 10 mg/kg/hour infusion during surgery . Later Inj Protamine was administered to reverse the effect of Heparin. After the completion of surgery patients were shifted to ICU and were assessed for blood loss at 4 hours and 24 hours after shifting. Indication for transfusion of PRBC was a haemoglobin level of <8 gm/dl. FFP was transfused if post-operative drain was >250 ml/hour in first hour. Platelet transfusion was indicated if platelets counts were <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 hours and 24 hours. Re-exploration of case was considered if the bleeding was >300 ml/hour in first 2 hours or if >200 ml/hour for 4 consecutive hours, 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 hours (**Figure 1)**.

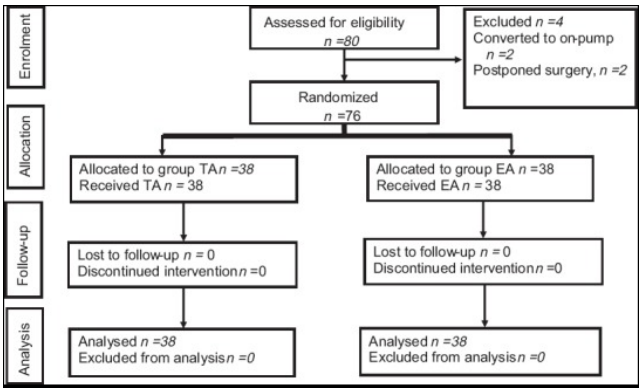

Figure 1: Randomization group allocation and assessment of patients.

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, Independent's tests were used and for nonparametric data Mann-Whitney u test were used. For categorical data, Chi-Square test or fisher's exact test were used. AP 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 and duration on CPB were also comparable in both groups (**Table 2**). Primary outcomes like bleeding at 4 hours, there was no significant difference between the groups but when total bleeding at 24 hours 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, whereas 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 and 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).**

Parameter	Group TA (n=40)	Group EACA (n=40)	p
Age (Years)	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 1: Baseline Demography.

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 2: Intra operative time and intervention.

Parameter	Group TA (n=40)	Group EACA (n=40)	P
Bleeding at 4 hours (ml)	190(90-260)	210(110-320)	0.0321
Total bleeding at 24 hours (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
Packed Red Blood Cell (PRBC); Fresh Frozen Plasma (FFP)			

Table 3: Primary and secondary outcome.

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 SCr	0	1	0.981
Myocardial Infarction (MI), Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), Serum Creatinine (SCr)			

Table 4: Post-operative complications.

Discussion

On pump CABG is associated with increased risk of post-operative bleeding compared to OPCAB [9,10] reason best attributable to use of CPB, which is associated with increased fibrinolysis and increased concentration of inflammatory mediators, which has urged researchers all around the world to investigate the probable role of antifibrinolytics in on pump cardiac surgeries [11]. 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 hours 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 [12]. Similar findings were obtained in a study comparing TA and EACA with placebo conducted by Karski et al. [13]. Chauhan et al. [14] and Faure et al. [15] 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 [16]. Therefore the role of these drugs in reducing the transfusion rate after on pump CABG is very significant. There were no differences in the rate of post-operative complications between the groups. 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 thromboembolic complications [17]. There are controversies with regards to the dosing of the drug. A high dose (20 mg/kg) TA is associated with increased risk of post-operative seizures and therefore a low dose (10 mg/kg) regime is recommended [18]. Armelin et al. compared the low dose and high dose TA regime and found no difference with respect to amount of post-operative blood loss or transfusion requirement [19]. 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 and 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 24 hours. Our study also re-emphasized the fact that neither of the drugs led to any additional risk of post-operative thrombotic complications and thus can potentially become a standard of care for blood conservation in patients undergoing on pump CABG.

References

1. Paparella D, Galeone A, Venneri MT, Coviello M, Scrascia G, et al. (2006) Activation of the coagulation system during coronary artery bypass grafting: Comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg 131: 290-297.
2. Bridges CR (2007) Valid comparisons of antifibrinolytic agents used in cardiac surgery. Circulation 115: 2790-2792.
3. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, et al. (2008) BART Investigators: A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 358: 2319-2331.
4. Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, et al. (2011) Update to the society of thoracic surgeons and the society of cardiovascular anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 91: 944-982.
5. Mehr-Aein A, Sadeghi M, Madanicivi M (2009) Does tranexamic acid reduce blood loss in off-pump coronary artery bypass? Asian Cardiovasc Thorac Ann 15: 285-289.
6. Greilich PE, Jessen ME, Satyanarayana N, Whitten CW, Nuttall GA, et al. (2009) The effect of epsilon-aminocaproic acid and aprotinin on fibrinolysis and blood loss in patients undergoing primary, isolated coronary artery bypass surgery: A randomized, double-blind, placebo-controlled, noninferiority trial. Anesth Analg 109: 15-24.

7. Sterns LP, Lillehei CW (1967) Effect of epsilon aminocaproic acid upon blood loss following open-heart surgery: An analysis of 340 patients. Can J Surg 10: 304-347.

8. Slaughter TF, Faghih F, Greenberg CS, Leslie JB, Sladen RN (1997) The effects of epsilon-aminocaproic acid on fibrinolysis and thrombin generation during cardiac surgery. Anesth Analg 85: 1221-1226.

9. Wei M, Jian K, Guo Z, Wang L, Jiang D, et al. (2006) Tranexamic acid reduces postoperative bleeding in off-pump coronary artery bypass grafting. Scand Cardiovasc J 40: 105-109.

10. Abu-Omar Y, Taggart DP (2009) The present status of off-pump coronary artery bypass grafting. Eur J Cardiothorac Surg 36: 312-321.

11. Mariani MA, Gu YJ, Boonstra PW, Grandjean JG, van Oeveren W, et al. (1999) Procoagulant activity after off-pump coronary operation: Is the current anticoagulation adequate? Ann Thorac Surg 67 :1370-1375.

12. Dhir A (2013) Antifibrinolytics in cardiac surgery. Ann Card Anesth 16: 117-125.

13. Karski JM, Teasolale SJ, Norma PH (1993) Prevention of post bypass bleeding with tranexamic acid and epsilon aminocaproic acid. J Cardiothorac Vasc Anesth 7: 431-435.

14. Chauhan S, Gharde P, Bisoi A, Kale S, Kiran U (2004) A comparison of aminocaproic acid and tranexamic acid in adult cardiac surgery. Ann Card Anaesth 7: 40-43.

15. Falana O, Patel G (2014) Efficacy and safety of tranexamic acid versus aminocaproic acid in cardiovascular surgery. Ann Pharmacother 48: 1563-1569.

16. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, et al. (2002) Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Sure 74: 1180-1186.

17. Hardy JF, Belisle S, Dupont C, Harel F, Robitaille D, et al. (1998) Prophylactic tranexemic acid andepsilon aminocaproic acid for primary myocardial revascularization. Ann Thorac Surg 65: 371-376.

18. Manji RA, Grocott HP, Leake J, Ariano RE, Manji JS, et al. (2012) Seizures following cardiac surgery: The impact of tranexamic acid and other risk factors. Can J Anest 59: 6-13.

19. Armellin G, Vinciguerra A, Bonato R, Pittarello D, Giron GP (2004) Tranexamic acid in primary CABG surgery: High versus low dose. Minerva Anestesiol 70: 97-107.