

Antifibrinolytics: e-Aminocaproic acid, Tranexamic Acid and Aprotinin

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Citation

J Levy. *Antifibrinolytics: e-Aminocaproic acid, Tranexamic Acid and Aprotinin*. The Internet Journal of Anesthesiology. 1996 Volume 1 Number 2.

Abstract

INTRODUCTION

Pharmacologic approaches to reduce bleeding and transfusion in cardiac surgical patients are based on either preventing the defects associated with the cardiopulmonary bypass CPB induced coagulopathy. Different pharmacologic agents have been reported, however the currently accepted pharmacologic interventions are based on using a protease inhibitor, aprotinin, or lysine analogs to inhibit fibrinolysis. These agents will be reviewed.

LYSINE ANALOGS

e-aminocaproic acid (EACA, Amicar) and its analogue, tranexamic acid (TA) are derivatives of the amino acid lysine. Both of these drugs inhibit the proteolytic activity of plasmin and the conversion of plasminogen to plasmin by plasminogen activators. Plasmin cleaves fibrinogen and a series of other proteins involved in coagulation. Tranexamic acid is 6 to 10 times more potent than e-aminocaproic acid. Most of the early studies using antifibrinolytic agents showed decreased mediastinal drainage in patients treated with EACA. However, many of these studies lacked controls, were retrospective, and not blinded ^{1,2}.

In 350 patients undergoing coronary artery bypass grafting (CABG), Del Rossi reported using a low dose of EACA a significant decrease in mediastinal drainage and red blood cell (RBC) transfusion with no difference in myocardial infarction (MI) or stroke ³. Vander Salm recently reported a reduction in chest tube drainage in 51 patients who received EACA ⁴. In addition, there were no differences in platelet function between EACA and the placebo group, and no differences in blood transfusion. Horrow later studied TA given in a prophylactic manner prior to skin incision for primary CABG surgery ⁵. The 12 hour postop blood loss was 496 ml in the TA group compared to 750 ml in the placebo

group. However, transfusions were not different. In another study they again found decreased chest tube drainage in patients receiving TA compared to those receiving placebo, but found no increased benefit by administering DDAVP concurrently ⁶.

In the literature there have been a small number of thrombotic complications between patients receiving lysine analogs. Although the design of these studies have not been routinely prospective, the incidence of these complications in routine CABG is low, and a small number of patients have been studied. Prospective studies evaluating safety issues including the risk of perioperative MI, graft patency, and renal dysfunction still need to be studied. TA is approved for use in the US to prevent bleeding in patients with hereditary angioedema undergoing teeth extraction, but has no FDA indication for use in CPB. Most studies report lysine analogues in first-time CABG where the risk of bleeding is low, and not in complex cases.

APROTININ

Aprotinin (Trasylo) is a serine protease inhibitor derived from bovine lung that inhibits trypsin, chymotrypsin, plasmin, tissue plasminogen activator, and kallikrein. Although aprotinin was studied in the 1960's, low doses were evaluated in an effort to treat bleeding after cardiac surgery rather than to prevent it. However, it was not until the late 1980's that prophylactic use was reported. In 1987 Van Oeveren reported a 47% reduction in blood loss in patients receiving aprotinin during CABG surgery. In 22 patients having reoperations with bubble oxygenators, Royston developed a pharmacologic approach to inhibit inflammatory responses during CPB administering a loading dose of 2 million units of aprotinin following intubation, and a continuous infusion of 500,000 units/hour with a CPB pump prime dose of 2 million units. This has become known as the

high dose or Hammersmith regimen. In patients receiving aprotinin, chest tube drainage was 286 ml as compared to 1509 ml in the controls ⁸. In a subsequent study of 80 patients undergoing primary coronary bypass surgery, patients receiving aprotinin bled 46% less than controls, receiving fewer units of packed RBC's (13 units vs. 75 units, aprotinin vs. placebo), and had no significant prolongation of their bleeding times, suggesting a platelet preserving effect of aprotinin independent of its antifibrinolytic properties ⁹.

Multiple other studies supported aprotinin's efficacy. Dietrich found decreased blood loss in patients receiving aprotinin as compared to those receiving placebo (738 ml vs. 1431 ml) for primary CABG ¹⁰. He also reported less formation of thrombin, fibrin, split products, and D-dimers in patients receiving aprotinin. Separate studies by Blauhut, Havel, Lemmer, and Marx have all confirmed decreased blood loss in patients receiving aprotinin at high doses ^{11,12,13,14}. Aprotinin also reduced blood loss 49-75% and transfusion requirements from 49-77% in three studies in patients receiving aspirin.

In redo CABG patients, Cosgrove reported 171 patients who received either high dose aprotinin (Hammersmith dose), low dose aprotinin (half Hammersmith dose), or placebo ¹⁶. They found that low dose aprotinin was as effective as high dose aprotinin in decreasing blood loss and blood transfusion requirements. Levy also reported the use of four different treatment groups in 287 patients undergoing repeat CABG surgery ¹⁹. Transfusion of allogenic packed RBC's was significantly less in the aprotinin-treated patients compared to the placebo (high dose: 1.6 units, low dose: 1.6 units, pump prime only: 2.5 units, placebo: 3.4 units), with even greater reductions in total blood product exposure in high dose and half dose groups compared to placebo or pump prime cohorts. There were no differences in treatment groups for the incidence of perioperative MI, and the incidence of stroke was lower in the aprotinin treated patients.

The precise mechanism of action and optimal dose of aprotinin in reducing blood loss and transfusion requirement is not clear. Further studies are needed to reveal how this drug decreases blood loss in patients undergoing CPB. Cosgrove suggested a trend towards a higher incidence of MI in the aprotinin treated groups, although they were not statistically significant ¹⁶. Other studies have not found any statistical differences in the incidence of these complications. Potentially any drug that decreases bleeding

and transfusion requirements has the potential to affect graft patency. Bidstrup, Havel, and Lemmer found no significant difference in the patency of grafted vessels when examined postoperatively ^{13,15,17}. Recently, a large multicenter study of patients undergoing primary CABG surgery in the US has shown no difference in graft patency or MI in aprotinin vs. placebo treated patients.

COMPARISON STUDIES

There is little data to compare the efficacy and safety of pharmacological agents available for reducing allogenic blood administration in cardiac surgical patients. In a retrospective study comparing aprotinin to EACA in high risk cardiac surgery patients, Van Norman reported reductions in transfusion requirements in the patients who received aprotinin and found it was a cost effective strategy ²². Another trial compared dipyrimdamole, TA, and aprotinin in 60 CABG patients. This study used a 2 million unit pump prime only dose of aprotinin. TA and aprotinin both significantly reduced postoperative blood loss but did not affect the transfusion rates although the investigators studied only 15 patients in each group. Another recent study compared TA to a pump prime only dose of aprotinin. Both drugs decreased blood losses compared to a control group but the transfusion trigger was a hematocrit of 30% and only median transfused volumes were compared.

SUMMARY

The use of lysine analogs (EACA or TA) in cardiac surgical patients results in less chest tube drainage but significant decreases in blood product transfusion requirements have not been consistently documented in blinded, placebo controlled studies. Despite their widespread application, carefully controlled studies with safety data regarding EACA and TA is limited. Aprotinin has a different mechanism of action and may attenuate other aspects of the inflammatory response to CPB. Aprotinin has been demonstrated to be highly effective in reducing bleeding and transfusion requirements in high risk patients undergoing repeat median sternotomy or in patients who are taking aspirin. Results from multicenter studies of aprotinin show there is no greater risk of early graft thrombosis, MI, or renal failure in aprotinin treated patients. The incidence of stroke was actually significantly lower in aprotinin treated patients ²⁴. Prospective well designed placebo controlled studies are needed to determine what are the most cost effective modalities for decreasing bleeding and transfusion requirements in cardiac surgical patients.

For more information on Aprotinin (Trasylol) please click [here](#).

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