COMPARISON OF THE EFFICACY OF LOW-DOSE APROTININ, EPSILON-AMINOCAPROIC, AND TRANEXAMIC ACID FOR CORONARY ARTERY BYPASS OPERATIONS

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One hundred and forty-eight patients undergoing primary myocardial revascularization were randomized to receive either low-dose aprotinin, aminocaproic acid, or tranexamic acid. An additional 50 patients, operated upon during the same time frame, served as the controls. All patients had been taking 325 mg of aspirin within 48 h before operation. All three drug regimens reduced the requirements for blood products and postoperative bleeding after coronary artery bypass. Low-dose aprotinin was more effective than epsilon-aminocaproic acid in reducing mediastinal blood loss, otherwise there were no differences in treatment outcomes between the drug regimens. There were no thrombotic-related complications associated with the use of antifibrinolytics. We conclude that all three treatment regimens reduced the need for blood products and the incidence of postoperative hemorrhage after myocardial revascularization.

ANTIFIBRINOLYTIC DRUG THERAPY has been shown to reduce the incidence of postoperative hemorrhage after open heart operations and the need for blood transfusions.1-9 The routine administration of these medications is becoming increasingly attractive because of the widespread use of antiplatelet drugs, the increasing number of patients requiring urgent surgery who are receiving or have recently received anticoagulation, and increased awareness of the risks of blood transfusions.

The use of antifibrinolytic drugs, for patients undergoing cardiac surgery, has become almost routine at our institution. However, the cost of administering these drugs may be substantial, particularly when employing the high-dose aprotinin drug regimen recommended by Royston and colleagues.1 Following our initial experience with high-dose aprotinin, our institution developed a low-dose aprotinin regimen that appeared to reduce blood loss after operation, was more cost effective than the high-dose regimen, and alleviated some of our concerns about the potential effects of high-dose aprotinin on graft patency after coronary artery bypass operations.2,10 The cardiac group also recently has gained experience with the use of epsilon-aminocaproic acid and tranexamic acid. The selection of the drug regimen, however, has always been based on the preference of the surgeon or the anesthesiologist. In order to determine whether there is any advantage in selecting a particular drug regimen, we designed this clinical trial to compare the efficacy of low-dose aprotinin, epsilonaminocaproic acid, and tranexamic acid for the prevention of bleeding after coronary artery bypass operations.

Patients and Methods

One hundred and ninety-eight patients undergoing coronary artery bypass were entered into the study. The study had been approved by the hospital's ethics committee. One hundred and forty-eight patients were randomized to receive one
of the three drug regimens. Fifty additional patients, during the same time frame, were selected to serve as the controls. The control group met the inclusion criteria for the study.

Inclusion and Exclusion Criteria
Elective and urgent patients were included in the study if they required at least three bypass grafts and if they had been taking 325 mg of aspirin within 48 h prior to operation. Patients were excluded if they had been receiving platelet-altering medication in addition to aspirin, if they were receiving intravenous heparin or had received streptokinase within 48 h before surgery, if they had an anergy to one of the treatment regimens, or if they required less than three bypass grafts based on the results of their cardiac catheterization. An screening was performed by three clinical research nurses.

Randomization and Preparation of the Antifibrinolytic Drug Regimens
Patients were randomized by the hospital pharmacist to one of the three treatment regimens when they were on can to the operating room. A random number table was used to select one of the drug regimens which included low-dose aprotinin, epsilon-aminocaproic acid, or tranexamic acid. The drug was then prepared in the hospital pharmacy, issued an identification code, and sent to the operating room. The code was broken by the pharmacist upon completion of the study.

The loading dose for an three drug regimens was administered after the induction of anesthesia and before cardiopulmonary bypass. An hourly maintenance dose was then infused until the termination of cardiopulmonary bypass. The low-dose aprotinin regimen consisted of a 200,000-KIU loading dose and then 200,000 KIU infused hourly during cardiopulmonary bypass. Patients randomized to epsilon-aminocaproic acid received a 5-gram loading dose and then 1 g/Ih on bypass, while those patients randomized to tranexamic acid received a loading dose of 10 mg/kg body weight followed by 1 mg/kg/h during bypass.

Operative Regimen
Anesthetic premedication consisted of sublingual lorazepam 1-2 mg 90 min prior to induction and then intramuscular morphine 0.1-0.15 mg/kg and perphenazine 2.5 mg 60 min prior to induction. A balanced anesthetic technique was employed that consisted of sufentanil 5-8 pg/kg, isoflurane 0.25%-1.5%, oxygen, and pancuronium. A radial artery line was inserted before anesthesia and a thermodilution pulmonary artery catheter was inserted after induction. Other routine monitors included pulse oximetry, capnography, EKG (leads II and V 5), nasopharyngeal temperature, and urine output.

Heparin was administered in a dose of 4 mg/kg before bypass and then the activated clotting time was monitored and maintained above 480 s throughout the duration of bypass. Mild hypothermia 30-32°C was employed in most patients, and an patients were perfused with a roner pump and a membrane oxygenator. The heart was arrested in an patients with blood cardioplegia, administered by a Shiley-Buckberg cardioplegia administration set (Shiley Corp.; Irvine, CA) that delivered the cardioplegia in a ratio of four parts blood to one part crystalloid. The only additive to the cardioplegia was potassium in a concentration that would provide 22 meq K/L for high-dose potassium and 7 meq K/L for low-dose potassium. Cardioplegia was administered as a continuous infusion when warm blood was used for myocardial protection or intermittently at 8°C when cold blood cardioplegia was utilized for myocardial protection. A combination of internal thoracic arteries and vein bypass grafts were used for coronary artery bypass. The proximal anastomoses were performed under a single cross-clamp or with the aid of a side-biting clamp, the technique being at the discretion of the surgeon.

Postoperative Blood Loss and Transfusion of Blood Products
Postoperative blood loss was defined as the total blood loss from the mediastinal and pleural chest tubes after leaving the operating room and until chest tube removal. Transfusion of blood products was defined as the administration of packed red blood cens, plasma, or a unit of platelets. The transfusion of blood products was at the discretion of the surgeon. Generally, red blood cens were not transfused unless the hemoglobin fell below 80 g/L.

Statistical Analysis
Parametric nominal data were compared between groups using analysis of variance. Frequency data
were compared using the chi-square test. The results have been reported as the arithmetic mean ± standard error of the mean.

Results

Forty-eight patients were randomized to receive low-dose aprotinin, 44 patients to epsilon-aminocaproic acid, and 56 patients to tranexamic acid. Fifty patients served as the controls.

The patient profiles were similar with respect to age, New York Heart Association classification, ejection fraction, number of grafts, use of the internal thoracic artery, and intraoperative variables (Table 1).

Postoperative Bleeding and Use of Blood Products

The total mediastinal blood loss, from the time the patient left the operating room until chest tube removal, was significantly lower in all treatment groups when compared with the control group (Table 2). Low-dose aprotinin was more effective than epsilon-aminocaproic acid in preventing hemorrhage after operation (P < 0.04), otherwise there was no other difference in the efficacy between the treatment regimens.

The total transfusion of blood products was significantly lower in the treatment groups as was the transfusion requirements for most of the individual blood products (Table 2). There was no difference in efficacy between treatment groups.

Complications Following Operation

There was only one non-hemodynamically significant myocardial infarction diagnosed by enzyme and EKG criteria in a patient receiving aminocaproic acid. The release of CPK-MB was similar in all groups, measuring 12 ±1.2 IU/L in the controls, 20 ±1.4 IU/L in those patients that had received low-dose aprotinin, 16 ±1.8 IU/L following the use of epsilon-aminocaproic acid, and 19 ±1.6 IU/L in those patients that had received tranexamic acid. There were no other significant complications after operation.

Table 1. Patient profiles.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Low-dose aprotinin</th>
<th>Epsilon-aminocaproic acid</th>
<th>Tranexami acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>63 ±1.3*</td>
<td>63 ±1.4</td>
<td>62.1±1.6</td>
<td>62±1.3</td>
</tr>
<tr>
<td>Preop NYHA class</td>
<td>3.1±0.07</td>
<td>3.1±0.08</td>
<td>3.0±0.08</td>
<td>3.0±0.06</td>
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<td>Preop EF (%)</td>
<td>58±2.4</td>
<td>62±2.0</td>
<td>60±2.0</td>
<td>59±1.2</td>
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<tr>
<td>Bypasses (n)</td>
<td>3.7±1.01</td>
<td>3.6±1.01</td>
<td>3.4±1.01</td>
<td>3.2±0.07</td>
</tr>
<tr>
<td>Mammary grafts (n)</td>
<td>1.2±1.01</td>
<td>1.1±0.08</td>
<td>1.2±1.01</td>
<td>1.1±0.08</td>
</tr>
<tr>
<td>Clamp time (min)</td>
<td>60±1.2</td>
<td>62±1.3</td>
<td>64±1.3</td>
<td>59±1.8</td>
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<tr>
<td>Bypass time (min)</td>
<td>99±3.4</td>
<td>108±4.5</td>
<td>100±4.1</td>
<td>100±2.8</td>
</tr>
<tr>
<td>OR time (min)</td>
<td>204±5.9</td>
<td>229±8.0</td>
<td>210±7.4</td>
<td>217±4.8</td>
</tr>
</tbody>
</table>

* ±: standard error of the mean.

NYHA = New York Heart Association classification; EF = ejection fraction; OR = operating room.

Table 2. Postoperative bleeding and usage of blood products.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Low-dose aprotinin</th>
<th>P value</th>
<th>Epsilon-aminocaproic acid</th>
<th>P value</th>
<th>Tranexami acid</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood loss (mL)</td>
<td>798±68*</td>
<td>515±1.49</td>
<td>&lt;0.001</td>
<td>643±40</td>
<td>&lt;0.05</td>
<td>535±45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total blood products (units/pt)</td>
<td>1.7±0.5</td>
<td>0.5±0.3</td>
<td>&lt;0.04</td>
<td>0.32±1.13</td>
<td>&lt;0.01</td>
<td>0.38±0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Red cells (units/pt)</td>
<td>0.9±0.2</td>
<td>0.25±0.08</td>
<td>&lt;0.003</td>
<td>0.27±0.1</td>
<td>&lt;0.007</td>
<td>0.2±0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets (units/pt)</td>
<td>0.5±0.3</td>
<td>0.17±0.17</td>
<td>&lt;0.2</td>
<td>0</td>
<td>&lt;0.05</td>
<td>0.18±0.18</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Plasma (units/pt)</td>
<td>0.2±0.1</td>
<td>0.08±0.08</td>
<td>&lt;0.3</td>
<td>0.045±0.045</td>
<td>&lt;0.1</td>
<td>0</td>
<td>&lt;0.02</td>
</tr>
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</table>

±: standard error of the mean. PI = patient.

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Antifibrinolytics were initially used in our center for those patients undergoing repeat cardiac operations. More recently, however, we have found that the use of this group of drugs is also beneficial in patients who have been taking aspirin before surgery because they have an increased risk of postoperative hemorrhage.\textsuperscript{11-14} Our patient population had all been taking 325 mg of aspirin daily within 48 h before operation. They had similar clamp times, bypass times, total operating room times, and all patients received one or more internal thoracic artery grafts. However, despite these similarities, all patients in the treatment groups had significantly less postoperative mediastinal drainage and received less blood products than the control group. The only advantage between treatment groups was related to the total mediastinal blood loss after operation which was lower in those patients that had received low-dose aprotinin.

Aprotinin

Aprotinin is a serine-proteinase inhibitor isolated from bovine lung. The activity has usually been expressed in plasma kallikrein units because the dosage was extrapolated from the concentration of aprotinin necessary to inhibit plasma kallikrein.\textsuperscript{IS} The kallikrein inhibition dosage regimen or high-dose regimen for cardiac operations described by Royston and colleagues\textsuperscript{1} consists of a 2,000,000-KIU loading dose, an additional 2,000,000 KIU added to the pump prime, and 500,000 KIU intravenously per hour while on bypass. This dose may not be required, however, to reduce mediastinal bleeding after heart surgery because much smaller doses inhibit plasmin\textsuperscript{16} and because aprotinin also preserves platelet function.\textsuperscript{17} Low-dose aprotinin regimens have been used by a number of investigators and have for the most part been successful in reducing postoperative hemorrhage. Cosgrove and colleagues\textsuperscript{2} compared the Hammersmith dosage regimen with 2,000,000 KIU added to the pump prime. The total blood loss was significantly greater after operation in those patients receiving the low-dose regimen. The study design, however, did not contain a control group and the blood loss was higher than one would normally expect after the use of aprotinin, measuring 709 ± 557 cc after high-dose aprotinin and 959 ± 627 cc after the low-dose regimen. Hong\textsuperscript{26} compared high-dose aprotinin with two other groups receiving either 2,000,000 KID or 1,000,000 KIU added to the pump prime. The lower dose was less efficient in reducing mediastinal blood loss after cardiac operations. The blood loss, however, was exceptionally low in all groups, measuring 165 ± 70 cc during the first 12 hours after high-dose aprotinin, 154 ± 56 cc after low-dose aprotinin, and 291 ± 78 cc in the control group. There were only 28 patients in the study; a larger cohort may well have detected a beneficial effect of the low-dose regimen because the mediastinal drainage was very similar between the treated patients. Hardy\textsuperscript{27} employed a loading dose of 200,000 KIU and then administered 100,000 KID/h. There was no significant difference between the groups, but the sample size was too small to be certain that the study design had not introduced a Type II statistical error since mediastinal bleeding was lower after the low-dose regimen.

In our study, we lowered the dose below previously reported dosage regimens. The loading prime, omitting the loading dose recommended by Hammersmith Hospital, and then infusing 500,000 KIU/h. Carrel\textsuperscript{20} and Benmosbah\textsuperscript{21} reported that a single dose of 2,000,000 KIU added to the pump prime was as effective as the high-dose regimen while Schonberger\textsuperscript{22} reduced the dose even further. He reported that half this dose (1,000,000 KID) reduced blood loss when administered to the pump prime in patients taking low-dose aspirin before operation. Covin\textsuperscript{023} determined that 1,000,000 KID (half the Hammersmith loading dose) and 500,000 KIU/h for the duration of cardiopulmonary bypass reduced postoperative mediastinal drainage without the need for the addition of aprotinin to the pump prime, while Isetta\textsuperscript{24} decreased postoperative blood loss by administering 500,000 KIU during induction (one-quarter of the Hammersmith loading dose) and then 500,000 KIU/h until the end of bypass.

Not all low-dose regimens have been effective. Schopf\textsuperscript{2s} compared the Hammersmith dosage regimen with 2,000,000 KIU added to the pump prime. The total blood loss was significantly greater after operation in those patients receiving the low-dose regimen. The study design, however, did not contain a control group and the blood loss was higher than one would normally expect after the use of aprotinin, measuring 709 ± 557 cc after high-dose aprotinin and 959 ± 627 cc after the low-dose regimen. Hong\textsuperscript{26} compared high-dose aprotinin with two other groups receiving either 2,000,000 KID or 1,000,000 KIU added to the pump prime. The lower dose was less efficient in reducing mediastinal blood loss after cardiac operations. The blood loss, however, was exceptionally low in all groups, measuring 165 ± 70 cc during the first 12 hours after high-dose aprotinin, 154 ± 56 cc after low-dose aprotinin, and 291 ± 78 cc in the control group. There were only 28 patients in the study; a larger cohort may well have detected a beneficial effect of the low-dose regimen because the mediastinal drainage was very similar between the treated patients. Hardy\textsuperscript{27} employed a loading dose of 200,000 KIU and then administered 100,000 KID/h. There was no significant difference between the groups, but the sample size was too small to be certain that the study design had not introduced a Type II statistical error since mediastinal bleeding was lower after the low-dose regimen.

In our study, we lowered the dose below previously reported dosage regimens. The loading
dose was 200,000 KIU, and then 200,000 Kill was infused per hour while on bypass. This dose was extrapolated from a pilot study in which we attempted to determine a dose that would be more cost effective than the high-dose regimen and a dose that would be unlikely to be implicated as a cause of thrombotic-related complications after operation. 2.10 The fact that this dosage regimen was successful is most likely related to the protective effects of aprotinin on platelet function because the dose is well below the dose required to inhibit kallikrein or plasmin. The beneficial effects of aprotinin on platelet function (have been previously described in detail2S-30) are related to the preservation of the platelet membrane IB glycoprotein receptors, which are reduced by as much as 50% by cardiopulmonary bypass and are vital to normal platelet adhesion.

Epsilon-Aminocaproic Acid and Tranexamic Acid

Epsilon-aminocaproic acid and tranexamic acid are synthetic antifibrinolytic drugs that reversibly bind to plasminogen and plasmin. The reversible complex prevents these molecules from binding to fibrin, thus inactivating their proteolytic actions.31 In addition, these drugs indirectly preserve platelets by blocking plasmin-induced platelet activation.32 Both these drugs have been used to prevent bleeding after cardiac operations; the main difference between the two medications is that tranexamic acid is approximately ten times more potent than epsilon-aminocaproic acid.

Jordan9 reported the results of a retrospective study that compared transfusion requirements in 350 patients after coronary bypass or valve replacement. Half the group received epsilon-aminocaproic acid while the remainder served as the controls. The percentage of patients requiring red-blood cell transfusions in the treatment group was reduced by 53% and the transfusions of platelets by 66%. The number of reoperations for bleeding was reduced by 75%. Vander Salm3 randomized 60 patients to placebo or epsilon-aminocaproic acid. Postoperative platelet counts were higher in those patients receiving epsilon-aminocaproic acid, and mediastinal blood loss was significantly lower in treated patients. DelRossi33 prophylactically administered epsilon-aminocaproic acid to 170 patients. A similar number receiving saline served as the controls. The 24-h mediastinal blood loss and the requirements for blood transfusions were significantly lower in those patients receiving the anti fibrinolytic. Daily4 and Troianos5 made similar observations following randomized, double-blind, clinical trials. Daily,4 however, was also able to link the beneficial effects of epsilon-aminocaproic acid to the inhibition of fibrinolysis, by demonstrating a reduction in the circulating levels of D-dimers and fibrin split products.

Tranexamic acid has also been shown to reduce blood loss after cardiac operations when used prophylactically. Horrow6 randomized 38 patients to tranexamic acid or placebo. Fibrinolysis was increased in the control group, blood loss was greater after operation, and the control patients received more fresh frozen plasma. The reports from Browns and Roussou9 support the findings of this earlier study but also were able to demonstrate a reduced requirement for packed cells and platelet transfusions.

Comparative Clinical Trials

Isetta24 randomized 108 patients to receive low-dose aprotinin, tranexamic acid, or placebo. Blood loss and transfusion requirements were reduced in both treatment groups, but there did not appear to be any advantage of either drug regimen. Blauhut34 randomized patients to receive high-dose aprotinin or tranexamic acid. Aprotinin significantly reduced mediastinal blood loss and the number of transfused packed cells. Blood loss and transfusion requirements were lower in those patients receiving tranexamic acid, but neither outcome differed significantly from the control group or the aprotinin group. A larger sample size would most likely have demonstrated a significant effect for tranexamic acid since there were only 43 patients enrolled in the study. Ralley35 compared low-dose aprotinin with tranexamic acid in a blinded, placebo-controlled trial. Both treatment groups were equally effective in reducing mediastinal drainage after coronary artery bypass but the authors concluded that the routine use of these drugs was not cost effective since the treated groups spent an equal length of time in the intensive care unit and in hospital before discharge. Murkin36 compared high-dose aprotinin, low-dose aprotinin, and tranexamic in a non-placebo controlled trial. High-dose aprotinin and tranexamic acid were equally effective in reducing blood loss and transfusion requirements, and both drug regimens were more effective than low-dose
Aprotinin. The results of a meta-analysis were recently reported which reviewed the placebo-controlled antifibrinolytic drug trials after 1980 in the English literature. The analysis indicated that the prophylactic use of either aprotinin or an antifibrinolytic drug reduced postoperative blood loss and the need for transfusions, but there was no advantage of any particular drug regimen.

Complications Related to the Use of Prophylactic Drug Therapies

The greatest concern related to the prophylactic use of antifibrinolytic drug therapy is that this group of drugs may potentiate the risk of thrombosis which may not only be confined to early coronary artery graft occlusion but may result in an increased incidence of stroke, peripheral vascular occlusion, or deep venous thrombosis. The concerns, however, are probably unjustified. Not all manuscripts have reported the incidence of postoperative thrombotic complications, but those reports that have included this data have generally not demonstrated an increased incidence of thrombosis after anti fibrinolytic therapy. A few articles have actually focused on the effects of aprotinin on graft patency. Bidstrup and colleagues indicated that graft patency, determined by nuclear magnetic resonance, was 96.2% in those patients that had received high-dose aprotinin and 97.1% in the control group. Havel performed angiography, 7 to 10 days after coronary bypass, and demonstrated that patency was 93.8% after high-dose aprotinin as compared to 93.3% in the non-treated patients. Lemmer used ultrafast CT imaging to determine graft patency in a group of patients that were randomized to high-dose aprotinin or placebo. Patency was 92.0% in the aprotinin-treated patients and 95.1% in the placebo group (P < 0.248). Laublo also used ultrafast CT imaging to determine patency after coronary bypass, reporting a patency of 100% in the control group and 88.4% in the treatment group (P < 0.057). Although the patency was lower after high-dose aprotinin, risk factor analysis indicated that there were many smaller conduits in the aprotinin group and that the distal vessels were of poorer quality. The meta-analysis that was discussed earlier also failed to link aprotinin or antifibrinolytic drug therapy with an increased incidence of thrombosis.

Conclusion

Our data indicate that low-dose aprotinin, epsilon-aminocaproic acid, or tranexamic acid will reduce mediasternal bleeding and the need for transfusion in patients undergoing coronary artery bypass grafting. Interestingly, a much smaller dose of aprotinin than has been previously reported appears to protect patients from postoperative hemorrhage. The increased risk of hemorrhage after operation, particularly in those patients on aspirin prior to operation, concerns about the transmission of transfusion-related disease, and the cost and morbidity associated with reoperation for bleeding support the prophylactic use of an anti fibrinolytic drug regimen.

Acknowledgment

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References


