Hemostatic Effects of Tranexamic Acid and Desmopressin During Cardiac Surgery

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Background. Desmopressin-induced release of tissue plasminogen activator from endothelial cells may explain the absence of its hemostatic effect in patients undergoing cardiac surgery. Prior administration of the antifibrinolytic drug tranexamic acid might unmask such an effect, and combination therapy might thereby improve postoperative hemostasis.

Methods and Results. A double-blinded design randomly allocated 163 adult patients undergoing coronary revascularization, valve replacement, both procedures, or repair of atrial septal defect to four treatment groups: placebo, tranexamic acid given as 10 mg/kg over 30 minutes followed by 1 mg·kg⁻¹·hr⁻¹ for 12 hours initiated before skin incision, desmopressin given as 0.3 μg/kg over 20 minutes after protamine infusion, and both drugs. One surgeon performed all operations. Blood loss consisted of mediastinal tube drainage over 12 hours. Follow-up visits sought evidence of myocardial infarction and stroke. Desmopressin decreased neither the 12-hour blood loss nor the amount of homologous red cells transfused. Tranexamic acid alone significantly reduced 12-hour blood loss, by 30% (mean, 318 versus 453 ml; p<0.001), without enhancement by desmopressin. Tranexamic acid also decreased the proportion of patients receiving homologous blood within 12 hours of operation (8% versus 21%, p=0.024) and within 5 days of operation (22% versus 41%, p=0.011).

Conclusions. Desmopressin exerts no hemostatic effect, with or without prior administration of antifibrinolytic drug. Prophylactic tranexamic acid alone appears economical and safe in decreasing blood loss and transfusion requirement after cardiac surgery. (Circulation 1991;84:2063–2070)

Bleeding remains a significant complication of open-heart surgery. Fibrinolysis and platelet dysfunction attributed to extracorporeal circulation (ECC) contribute to bleeding after operation.¹ Hemostatic drugs are among the measures available to decrease bleeding and transfusion.² Aprotinin,³ desmopressin,⁴ and the lysine-analogue antifibrinolytic preparations ε-aminocaproic acid (EACA)⁵ and tranexamic acid⁶ may provide salutary hemostatic effects.

Initial reports of decreased blood loss and transfusion requirements with desmopressin⁷ have not been substantiated in adult⁸,⁹ or pediatric¹⁰ populations. Desmopressin transiently releases tissue-type plasminogen activator from endothelial cells.¹¹ Plasminogen activator could augment an ECC-associated fibrinolytic state.¹¹,¹² Might augmented fibrinolysis, induced by release of tissue plasminogen activator, negate a salutary hemostatic effect of desmopressin? If so, then prior treatment with a potent antifibrinolytic should unmask a desmopressin-mediated decrease in bleeding and transfusion requirement.

We investigated the separate and combined hemostatic effects of tranexamic acid, a potent antifibrinolytic agent, and desmopressin during cardiac surgery in an effort to determine whether the salutary effect of tranexamic acid, which we found in a previous, separate investigation,⁶ could be surpassed with the combination of drugs.

Methods

Patients for elective cardiac operation performed by a single surgeon (M.D.S.) gave informed consent after institutional review board approval. Patients excluded from participation took warfarin or estrogens within 7 days of surgery; had active hematuria, a serum creatinine concentration of 2 mg·dl⁻¹ or
more, or a personal or family history of abnormal bleeding; or underwent intra-aortic balloon counter-pulsation. Patients receiving aspirin within 7 days of operation, heparin infusion within 8 hours, or non-steroidal anti-inflammatory medication within 3 days could participate but were randomized separately to permit even distribution among groups. Participation of these patients permits application of the study results to a representative population of elective surgical patients. The large number of patients enrolled in the study and separate randomization schedule limit any confounding effect of their inclusion on outcome variables. Enrolled patients underwent coronary revascularization, valve replacement, both procedures, or atrial septal defect repair.

**Group Assignments**

A table of random numbers determined patient allocation to one of four groups. The placebo group (group P) received saline infusions. A second group (group T) received tranexamic acid beginning after induction of anesthesia but before skin incision (loading dose, 10 mg·kg₁·hr⁻¹ over 30 minutes) followed by a 12-hour infusion of 1 mg·kg⁻¹·hr⁻¹. A third group (group D) received desmopressin acetate (0.3 μg·kg⁻¹·i.v. over 20 minutes) beginning after ECC following completion of protamine infusion. Patients in the fourth group (group B) received both tranexamic acid and desmopressin in identical fashion to groups T and D. Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions. Actual group assignments became known months after patient participation ended.

**Anticoagulation**

Bovine lung heparin (Organon, West Orange, N.J.) (400 units·kg⁻¹) provided anticoagulation for ECC. Automated activated coagulation time (Hemochron, International Technidyne Corp., Edison, N.J.) greater than 480 seconds, determined in duplicate every 30 minutes, ensured continued anticoagulation. For ECC, nonoclusive roller pumps, membrane oxygenators, cold sanguinous cardioplegic arrest, and systemic hypothermia to 25°C were used. The ECC circuit initially contained 5,000 units of beef lung heparin in 2 l of clear fluid prime (Plasmalyte A solution, Baxter Healthcare Corp., Deerfield, Ill.). Termination of ECC required a distal esophageal temperature of 37°C or greater and urinary catheter temperature of 34°C or greater. After ECC, protamine (4 mg·kg⁻¹) neutralized heparin to obtain an activated coagulation time within 15 seconds of baseline.13 Infusion of residual blood from the extracorporeal circuit followed approximation of the sternal wound edges. A subsequent additional protamine infusion (30% of the initial dose) neutralized heparin in the pump blood and protected against heparin rebound,14 as confirmed by repeat activated coagulation time.

**Blood Loss**

The mass of blood collected via mediastinal drains over 12 hours constituted blood loss. No attempt was made to estimate blood loss before or during ECC, or before insertion of mediastinal drainage tubes. The study ignored estimates of irrigation fluid, sponge and suction container losses, and soaking of linens; all of these minor components of operative blood loss are notoriously inaccurate. Blood loss occurring between protamine infusion and mediastinal tube placement contributes trivially to overall blood loss (unpublished data, G. Gravlee). All mediastinal blood lost after initial heparin administration until termination of ECC was eventually returned to the patient via the ECC circuit. After ECC, a citrated autotransfusion drainage system (Pleur-evac, Deknatel, Queens Village, N.Y.) permitted return of shed blood to those patients experiencing initial rapid blood accumulation via mediastinal tubes.

**Transfusion**

Transfusion of packed red blood cells in the first 12 hours after surgery required one or more of the following: hematocrit less than 21% measured at least 1 hour after surgery, chest tube drainage of 250 ml·hr⁻¹ or more, or hematocrit less than 24% associated with hemodynamic signs of hypovolemia, defined as heart rate greater than 110 beats per minute and pulmonary arterial diastolic pressure less than 10 mm Hg. Transfusion of fresh frozen plasma or platelets required brisk (250 ml·hr⁻¹ or more) bleeding and a strong suspicion or laboratory confirmation of deficiency in coagulation factors or decrease in platelet count, respectively. All red cell transfusions in the first 12 hours were weighed before administration. The weight of the filled container minus that of an empty bag (34 g) constituted the mass administered. After 12 hours, strict transfusion criteria no longer applied; clinician preference supervised. Each subsequent unit of packed red blood cells given to the patient contributed 300 g toward total transfusion mass.

**Coagulation Tests**

Before induction of anesthesia and again 2 hours after completion of initial protamine infusion, assessment of coagulation proceeded with measurement of activated partial thromboplastin time, manual platelet count, plasma fibrinogen,15 factor VIII coagulant activity, serum fibrin-fibrinogen—related antigen (latex agglutination, Thrombo-Welleco Test, Burroughs Wellcome, Research Triangle Park, N.C.), and latex agglutination D-dimer (D-di, American Bioproducts, Parsippany, N.J.). D-dimer is a specific breakdown product of factor XIIa–stabilized, cross-linked fibrin. Template bleeding times were omitted because of difficulty with patient access.
TABLE 1. Demographic and Other Descriptors of Patient Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Desmopressin</th>
<th>Tranexamic acid</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>44</td>
<td>38</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64±10</td>
<td>63±11</td>
<td>65±11</td>
<td>63±9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77±15</td>
<td>74±15</td>
<td>80±23</td>
<td>82±16</td>
</tr>
<tr>
<td>Height (in.)</td>
<td>67±4</td>
<td>66±3</td>
<td>67±3</td>
<td>68±4</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9±0.24</td>
<td>1.8±0.22</td>
<td>1.8±0.19</td>
<td>1.9±0.23</td>
</tr>
<tr>
<td>ACB</td>
<td>36 (82%)</td>
<td>32 (84%)</td>
<td>26* (70%)</td>
<td>34 (85%)</td>
</tr>
<tr>
<td>Valve</td>
<td>6</td>
<td>3</td>
<td>6†</td>
<td>6</td>
</tr>
<tr>
<td>Combined</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>ASD</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Repeat operation</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>ECC (min)</td>
<td>98±33</td>
<td>92±34</td>
<td>87±40</td>
<td>92±31</td>
</tr>
<tr>
<td>Pump blood (g)</td>
<td>660±137</td>
<td>697±173</td>
<td>689±171</td>
<td>649±110</td>
</tr>
<tr>
<td>Shed blood given</td>
<td>17</td>
<td>10</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Shed blood (g)†</td>
<td>386 (149–860)</td>
<td>418 (200–650)</td>
<td>343 (156–505)</td>
<td>185 (164–385)</td>
</tr>
<tr>
<td>Initial Hct (%)</td>
<td>37±5</td>
<td>37±5</td>
<td>36±5</td>
<td>36±4</td>
</tr>
<tr>
<td>Hct after ECC (%)</td>
<td>25±5</td>
<td>24±4</td>
<td>25±4</td>
<td>26±4</td>
</tr>
<tr>
<td>Hct in ICU (%)</td>
<td>26±5</td>
<td>25±5</td>
<td>27±4</td>
<td>27±4</td>
</tr>
</tbody>
</table>

Entries are number of patients (percent), mean±SD, or median (range).
BSA, body surface area; ACB, aortocoronary bypass grafting; Valve, valve replacement; Combined, simultaneous valve replacement and ACB; ASD, repair of atrial septal defect; ECC, duration of extracorporeal circulation; Pump blood, mass of pump fluid infused after sternotomy; Shed blood, mass of mediastinal shed blood infused after surgery; Hct, packed red cell volume before incision (initial), after protamine administration (after ECC), and 2 hours after protamine administration (in ICU).

*Includes one combined coronary revascularization with carotid endarterectomy.
†Includes one open mitral commissurotomy.
‡Median and range of shed blood mass are only for those patients who received shed blood, the number of whom is indicated in the row immediately above.

Follow-up

Daily visits to each patient sought evidence of myocardial infarction and stroke. Myocardial infarction required new Q waves on the electrocardiogram or creatine kinase-MB more than 19 units·L⁻¹·h⁻¹. Stroke diagnosis required a new focal deficit confirmed by computed tomography.

Data Analysis

For normally distributed data, two-way analysis of variance interpreted the data, using as factors 1) administration of tranexamic acid, 2) administration of desmopressin, and 3) interaction term. This analysis automatically separates out the independent contribution of each single drug and its contribution to group B data, expressing any remaining effect as an interaction term. This interaction term thus denotes synergism or antagonism of the two drugs on the measured parameter. Except in cases where an interaction is known to be absent, interaction terms are included in a two-way analysis of variance model, with any remaining effect attributed to error. Where appropriate, significant effects among the four groups were explored further with the Newman-Keuls multiple range test. Parametric data are reported as mean±SD.

Blood loss data did not conform to the normal distribution. However, logarithmic transformation yielded normally distributed values, permitting two-way analysis of variance on these transformed data, which are reported as mean and 95% confidence intervals of the back-transformed values.

Paired Student's t test compared postoperative versus preoperative coagulation data. Comparisons among the four groups of nonparametric data were done by Kruskal-Wallis analysis. Median and range statistics report nonparametric data.

Frequency data underwent contingency table analysis using likelihood ratio χ² statistics. Compressed 2×2 frequency tables, which tested the separate effects of each drug, used Fisher's exact test. In a compressed table, the entries for groups B and T, for example, would be added columnwise, as are those for groups D and P, to test for an effect of tranexamic acid. Since compressed table analysis might produce spurious results by failing to separate individual drug effects in group B, multinomial logistic regression verified the results from analysis of compressed tabular data. This technique uses Wald statistics and the log-likelihood ratio test¹⁷ to determine whether tranexamic acid administration alone, desmopressin administration alone, and simultaneous administration of both agents affect the outcome frequency variable. All tests are two-tailed, with p<0.05 denoting significance.

Results

Of 163 patients enrolled, four did not complete the study. Two of these four patients, one in group P and one in group T, returned to the operating room for mediastinal exploration, upon which active bleeding
from a branch of an internal mammary artery graft was found in each case. A third patient (group D) displayed a new rash at the conclusion of surgery. The fourth (group B) could not be separated from ECC following a third operation for coronary occlusive disease despite patient grafts.

Demographic variables for the remaining 102 men and 57 women did not differ among groups. Table 1 displays these data by group, along with the duration of ECC, mass of pump blood transfused after ECC, the amount of mediastinal shed blood transfused, and hematocrits measured before skin incision, after termination of ECC, and upon arrival in the intensive care unit after surgery. None of these differed among groups.

Coagulation

Baseline coagulation studies did not differ among groups. Table 2 displays the aggregate data. Five patients exhibited positive fibrin-fibrinogen split products on baseline testing: three in group D, one in group T, and one in group P. This population of cardiac surgical patients, like other patients with cardiac disease, displayed elevated D-dimer concentrations before surgery. Activated partial thromboplastin time and factor VIII did not change with operation. Both platelet count and plasma fibrinogen displayed an expected decrease with hemodilution after operation compared with before (p<0.0001, paired t tests). Table 3 displays results of fibrin degradation product assays 2 hours after protamine infusion. Patients who received tranexamic acid, those in groups T and B, exhibited positive (10 μg · ml⁻¹ or more) fibrinogen-fibrin split products less frequently (p=0.0023, effect confirmed with multinomial logistic regression). Likewise, those patients had lower plasma D-dimer concentrations compared with patients who did not receive tranexamic acid (p=0.0001). Every patient with positive serum antigen fibrin-fibrinogen split products also displayed elevated D-dimer.

Blood Loss and Transfusion

Two-way analysis of variance indicated no effect of desmopressin on 12-hour mediastinal tube drainage. However, tranexamic acid administration strongly affected the mass of blood lost (Table 4). No additional savings in blood loss accrued from administration of both tranexamic acid and desmopressin. Overall, the 77 patients who received tranexamic acid bled 30% less than the 82 patients who did not receive tranexamic acid (Figure 1).

In the first 12 hours after surgery, 23 of the 159 patients received homologous red cell transfusions. By 5 days after surgery, 51 patients had received homologous blood. Desmopressin did not affect the number of patients receiving homologous red cells in the first 12 hours or the first 5 days (Table 5). However, tranexamic acid administered to 77 patients in groups T and B resulted in less frequent

### Table 2. Coagulation Tests Before Skin Incision and 2 Hours After Protamine

<table>
<thead>
<tr>
<th>Test</th>
<th>Placebo</th>
<th>Desmopressin</th>
<th>Tranexamic acid</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT (seconds above control)</td>
<td>3±8</td>
<td>6±12</td>
<td>3±7</td>
<td>6±18</td>
</tr>
<tr>
<td>Platelet count (10⁶·l⁻¹)</td>
<td>360±248</td>
<td>354±166</td>
<td>336±97</td>
<td>316±105*</td>
</tr>
<tr>
<td>Fibrinogen (mg·dl⁻¹)</td>
<td>253±83</td>
<td>253±84</td>
<td>244±74</td>
<td>245±94*</td>
</tr>
<tr>
<td>Factor VIII (% activity)</td>
<td>117±81</td>
<td>111±49</td>
<td>105±36</td>
<td>121±55</td>
</tr>
<tr>
<td>D-dimer (FEU)</td>
<td>0.89±1.8</td>
<td>1.3±2.0</td>
<td>1.5±1.9</td>
<td>0.81±0.73†</td>
</tr>
<tr>
<td>FSP≥10 μg · ml⁻¹</td>
<td>1/44</td>
<td>2/37§</td>
<td>1/37</td>
<td>0/40</td>
</tr>
</tbody>
</table>

Entries are mean±SD.

aPTT, activated partial thromboplastin time; FEU, fibrinogen equivalent units (normal <0.5); FSP, serum antigen fibrin-fibrinogen split products.

*P<0.0001 for after surgery compared to baseline.

‡P<0.05 for after surgery compared to baseline.

§One sample lost in processing.

¶Entries are number of patients (percent). Tranexamic acid affected the incidence of fibrin split products (p=0.0023) but desmopressin did not (p=NS).
TABLE 3. Mass of Blood (g) Drained Via Mediastinal Tubes Over 12 Hours

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean*</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>44</td>
<td>462</td>
<td>404–529</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>38</td>
<td>443</td>
<td>392–500</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>37</td>
<td>328</td>
<td>275–392</td>
</tr>
<tr>
<td>Both</td>
<td>40</td>
<td>310</td>
<td>271–355</td>
</tr>
</tbody>
</table>

Entries are grams of blood drained via mediastinal tubes over 12 hours. Values for the mean and 95% confidence interval of the log-normal distribution are back-calculated from the logarithmically transformed data.

*p Two-way analysis of variance shows an effect of tranexamic acid (p<0.0001), no effect of desmopressin (p=0.46), and no synergism or antagonism of the drugs (p=0.92).

administration of homologous blood in the first 12 hours (p=0.024) as well as in the first 5 postoperative days (p=0.011, Figure 2). Administration of both drugs did not impart an additional effect on the likelihood of transfusion when analyzed by compressed contingency tables (p=0.42 for 12-hour data; p=0.053 for 5-day data). In confirmation, a multiple logistic regression model identified tranexamic acid administration (p=0.0049), but not desmopressin or both drugs, as a significant predictor of blood transfusion in the first 5 days.

One patient (group P) received fresh frozen plasma. Another patient (group D) received platelet concentrates. A third patient (group P) received both. A fourth patient (group P) received one unit (550 g) of autologous blood donated days before operation, despite not satisfying criteria for red blood cell transfusion. Hematocrit on the fifth postoperative day (27.5±3.8%) did not differ among groups.

Complications

One patient (group P) returned to the hospital 6 weeks after discharge with deep vein thrombosis. No patient developed new perioperative myocardial infarction. Three patients developed cardiovascular difficulties following the first postoperative day. Ventricular dysfunction occurred on the second postoperative day in one patient (group B), pulmonary edema on the fifth postoperative day in a second patient (group T), and ventricular tachycardia on the fourth postoperative day in a third patient (group T). Repeat cardiac catheterization in the last patient revealed patent vein grafts but an occluded internal mammary artery graft.

Five patients suffered perioperative stroke, for an overall rate of 3%. Two patients (both in group D) awoke from anesthesia with hemiplegia; one had a history of prior transient ischemic attacks and was found at surgery to have a heavily calcified aorta. A third group D patient awoke intact but developed a dense paralysis on the fourth postoperative day. The fourth patient, who received both drugs, awoke intact but developed new atrial fibrillation with subsequent stroke on the fourth postoperative day. The fifth patient (group T) awoke intact after combined right carotid endarterectomy and coronary grafting but

FIGURE 1. Blood loss in grams via mediastinal drains over 12 hours by groups as defined in Table 4. Note that half the patients in each of the Desmo+ and Desmo− groups received tranexamic acid. Column height denotes mean. Error bars indicate the 95% confidence intervals back-calculated from the log-normal distribution. *p<0.0001.

TABLE 4. Frequency of Blood Transfusion After Operation

<table>
<thead>
<tr>
<th>Group</th>
<th>Yes</th>
<th>No</th>
<th>% No</th>
<th>Yes</th>
<th>No</th>
<th>% No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8</td>
<td>36</td>
<td>82</td>
<td>16</td>
<td>28</td>
<td>64</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>9</td>
<td>29</td>
<td>76</td>
<td>18</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>Tranexamic acid*</td>
<td>4</td>
<td>33</td>
<td>89</td>
<td>12</td>
<td>25</td>
<td>68</td>
</tr>
<tr>
<td>Both drugs*</td>
<td>2</td>
<td>38</td>
<td>95</td>
<td>5</td>
<td>35</td>
<td>95</td>
</tr>
<tr>
<td>Desmo (−)†</td>
<td>11</td>
<td>67</td>
<td>86</td>
<td>23</td>
<td>55</td>
<td>71</td>
</tr>
<tr>
<td>Desmo (+)†</td>
<td>12</td>
<td>69</td>
<td>85</td>
<td>28</td>
<td>53</td>
<td>65</td>
</tr>
<tr>
<td>TA (−)‡</td>
<td>17</td>
<td>65</td>
<td>79</td>
<td>34</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>TA (+)‡</td>
<td>6</td>
<td>71</td>
<td>92</td>
<td>17</td>
<td>60</td>
<td>78</td>
</tr>
</tbody>
</table>

Entries are number of patients who received (Yes) or did not receive (No) homologous blood. For the compressed tabular data, which appear below the separate group data, Desmo (−) comprises the placebo and tranexamic acid groups, and Desmo (+) contains groups receiving either desmopressin alone or both drugs. TA (−) comprises the placebo and desmopressin groups, and TA (+) contains groups receiving either tranexamic acid alone or both drugs. Administration of both drugs exerted no effect on blood transfusion above that of tranexamic acid alone at 12 hours (p=NS) or at 5 days (p=NS) via 2×2 table analysis.

†Desmopressin exerted no effect at 12 hours (p=NS) or at 5 days (p=NS).
‡Tranexamic acid decreased the incidence of blood transfusion at 12 hours (p=0.024) and at 5 days (p=0.011).
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...within variety of cardiac surgery. \(p=0.024; \)**p=0.011.

developed left hemiplegia 10 hours later. Table 6 summarizes these complication data.

**Discussion**

Ongoing thrombin activity\(^{19-21}\) and low-grade fibrinolysis\(^{2,22-23}\) accompany ECC. Early trials seeking hemostatic effects of antifibrinolytic medications after cardiac surgery lacked blinded or randomized designs.\(^ {24-27}\) Although more recent studies have used currently acceptable experimental methods, these have all investigated the hemostatic effect of EACA given after ECC, with mixed results.\(^ {5,28,29}\) The current study design featured prophylactic administration of an antifibrinolytic drug, tranexamic acid, anticipating that the etiology of a hemostatic diathermy may arise early during surgery. Tranexamic acid is approximately 10-fold more potent than EACA.

Recent attention has focused on desmopressin, an analogue of arginine vasopressin (antidiuretic hormone) that releases multimers of von Willebrand factor from endothelial cells. Desmopressin exerts a positive hemostatic effect in patients with hemophilia,\(^ {30}\) von Willebrand disease,\(^ {20}\) and uremia.\(^ {31}\) Initial reports showed a salutary effect on bleeding in patients undergoing more complicated cardiac surgery—valvular replacement or repeat sternotomy procedures\(^ {4}\)—or as a replacement for transfusion therapy in patients who bleed excessively after surgery.\(^ {7}\) However, Rocha et al\(^ {18}\) could not demonstrate a saving in either bleeding or blood administered in 100 adults undergoing valve replacement or repair of atrial septal defect. Seear et al\(^ {10}\) demonstrated no benefit of desmopressin in 60 children undergoing a variety of cardiac operations. Hackmann et al\(^ {9}\) confirmed no advantage of desmopressin as a hemostatic pharmaceutical for elective cardiac operations in 150 adults.

In agreement with most studies,\(^ {5-10,32}\) the current investigation demonstrated no effect of desmopressin on mediastinal drainage after surgery. The outcome data do demonstrate a salutary hemostatic effect of antifibrinolytic drug, also in agreement with recent investigations.\(^ {5,6}\) The current study further demonstrates, in two ways, the absence of potentiation of fibrinolysis after cardiac surgery by desmopressin. First, desmopressin did not affect the presence of fibrinogen-fibrin degradation products or D-dimer concentration. Second, establishment of ongoing antifibrinolytic therapy did not uncover a hemostatic effect of desmopressin over and above that provided by the antifibrinolytic agent alone, as documented by no synergism with tranexamic acid on 12-hour measured blood loss and on the proportion of patients who received homologous blood within 12 hours and within 5 days of operation. Near attainment of statistical significance in the 5-day comparison \(p=0.053\) suggests that a true effect might be uncovered with enrollment of additional patients. However, logistic regression analysis supports no effect of the combination of drugs. Furthermore, because antifibrinolytic inhibition of the transient desmopressin-induced release of tissue plasminogen activator affected neither 12-hour blood loss nor 12-hour transfusion requirement, it is reasonable not to challenge the absence of an effect on 5-day transfusion requirement. Thus, we conclude that administration of both drugs imparts no additional hemostatic effect. To ensure that inclusion of patients taking aspirin did not influence these results, data were reanalyzed by a three-way analysis of variance with the additional factor of recent aspirin ingestion as defined in “Methods.” Aspirin did not affect blood loss in the study patients.

This study measured blood loss by mass instead of by volume, thus affording two advantages. First, closed-system mass quantitation provides higher precision (1 part in 1,000) compared with closed-system volumetric measure (1 part in 10). Second, the mass of blood with a higher hematocrit will be greater than the mass of the same volume of more dilute blood and thus will better represent the greater loss of red cell volume. Since blood density varies between 1.03 and 1.04 g · mL\(^ {-1}\) (hematocrits of 20% and 30%, respectively),\(^ {33}\) this difference introduces less than 1% error should mass measurements be interpreted as volume.

By what mechanism might tranexamic acid provide decreased postoperative bleeding? Unlike other surgical procedures, in which patients exhibit decreased fibrinolysis after operation,\(^ {34}\) ECC induces a mild fibrinolytic state, which lasts several hours after operation.\(^ {1,12}\) Failure of full anticoagulating doses of heparin to limit thrombin activity during ECC, as evidenced by ongoing formation of fibrinopeptide-A,\(^ {19-21}\) may incite this fibrinolytic activity. The anticoagulation margin of safety in this study (activated

**TABLE 5. Incidence of Complications After Surgery**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Stroke</th>
<th>Cardiovascular</th>
<th>Myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>44</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>38</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>37</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Both drugs</td>
<td>40</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

\(n, \) number of patients in each group.

Entries are number of patients.
coagulation time more than 480 seconds instead of more than 400 seconds) ensured no coagulation activity in addition to that already documented.19 These patients exhibited no evidence of hypercoagulability despite inhibition of fibrinolytic activity during and after ECC.

Both fibrinolysis and partial platelet activation during ECC with subsequent platelet dysfunction may alter hemostasis after ECC.1,12 Since plasmin induces platelet activation, a potential role for lysine-analogue antifibrinolytic medications is to block plasmin receptors on platelets, inhibiting local fibrinolysis-induced partial platelet activation.35 Administration of tranexamic acid before ECC is associated with preserved platelet ADP and decreased bleeding after ECC.36 Aprotinin, a serine protease inhibitor with antifibrinolytic properties, preserves platelet glycoprotein receptors and platelet function after ECC.37 Whether antifibrinolytics exert hemostatic effects by platelet preservation, by inhibition of fibrinolysis, or by both mechanisms remains unknown.

Is tranexamic acid safe in patients with coronary artery occlusive disease? Theoretical considerations suggest that tranexamic acid may be associated with thrombosis and subsequent stroke, myocardial infarction, or deep vein thrombosis. Case reports of renal cortical necrosis from EACA dampened initial enthusiasm of antifibrinolytic therapy.38,39 However, prospective studies5,6,27,28,40,41 failed to confirm a thrombotic hazard from routine antifibrinolytic administration. In the current investigation, ethical considerations prevented subjecting patients to the additional risks of repeat cardiac catheterization to document graft patency after surgery. Theoretically, thrombotic complications of tranexamic acid should not occur during cardiac surgery; full systemic anticoagulation with heparin should protect these patients from a presumed thrombotic tendency of tranexamic acid.42 Normal coagulation does not return until approximately 12 hours after surgery,1 at which time tranexamic acid plasma levels have declined (plasma half-life, approximately 80 minutes).43 Although data from the current study on stroke and perioperative myocardial infarction are limited, they are consistent with data from other studies suggesting no association with routine administration of antifibrinolytics during cardiac surgery.5,6 The stroke rate for patients receiving tranexamic acid in this study (two of 77 patients, or 2.6%) compares favorably with those of other prospective studies of patients undergoing ECC (2.9%).44

The extent of savings in blood lost and blood transfused with tranexamic acid is not surpassed by savings reported with comparable prophylactic use of aprotinin.45 However, at $15 per patient, tranexamic acid costs considerably less than aprotinin (about $150 in the U.K.). Furthermore, aprotinin use complicates monitoring anticoagulation therapy during surgery with the activated coagulation time,46 whereas tranexamic acid does not interfere with this simple, inexpensive, widely used technique.

These data suggest that desmopressin-induced release of tissue plasminogen activator plays no role in desmopressin’s lack of hemostatic effect during cardiac surgery. These data also demonstrate that tranexamic acid decreases the incidence of fibrin degradation products, decreases blood loss after surgery, and decreases the likelihood of homologous blood transfusion. Tranexamic acid appears effective, safe, inexpensive, and convenient.

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References


KEY WORDS • antifibrinolytic agents • extracorporeal circulation • fibrin fibrinogen degradation products • hemostasis, surgical
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