APROTININ VERSUS DESMOPRESSIN FOR PATIENTS UNDERGOING OPERATIONS WITH CARDIOPULMONARY BYPASS

A double-blind placebo-controlled study

Background. **Aprotinin reduces blood loss in operations done with cardiopulmonary bypass, whereas the use of desmopressin remains controversial. We compared aprotinin, desmopressin, and placebo in a double-blind, randomized trial to evaluate bleeding and transfusion requirements.** *Methods and results.* **One hundred forty-nine patients (48 received aprotinin, 50 desmopressin, 51 placebo) were included. Blood loss and transfusion requirements were recorded and levels of Factor VIII coagulant activity, von Willebrand's factor, thrombin-antithrombin complexes, and D-dimer were measured. Overall blood loss was 195 ± 146 ml/m^2 in the aprotinin group, 400 ± 192 ml/m^2 in the desmopressin group, and 489 ± 361 ml/m^2 in the placebo group (95% confidence intervals: difference between desmopressin and aprotinin 98 to 312 ml/m^2, $p < 0.001$; difference between placebo and aprotinin 190 to 398 ml/m^2, $p < 0.001$). Twenty-six percent of patients treated with aprotinin, 66% of those treated with desmopressin, and 56% of those treated with placebo were given transfusion (95% confidence intervals: difference between aprotinin versus placebo plus desmopressin 51% to 71%, $p < 0.001$). Fibrinolytic activation throughout cardiopulmonary bypass was markedly higher with placebo or desmopressin administration. D-dimer level correlated with overall blood loss in patients receiving desmopressin or placebo, but not in those receiving aprotinin.** *Conclusion.* **Aprotinin administration reduces blood loss and transfusion requirements in cardiopulmonary bypass. This benefit may be explained by a lower activation of fibrinolysis. (J THORAC CARDIOVASC SURG 1995;110:1107-17)**

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Hemorrhage is a common and important problem in patients undergoing operations done with cardiopulmonary bypass (CPB) and carries a major risk of early and late complications. Continued concern about the risks of blood transfusions and the problems of occasional shortages of donor blood and increasing costs have stimulated interest in blood conservation. Risks include transfusion reactions, blood component alloimmunization, transmission of blood-borne viruses (human immunodeficiency virus, human T-cell leukemia virus type I, cytomegalovirus, hepatitis viruses),[1-2] and transfusion-associated graft-versus-host disease.[3]

The cause of increased nonsurgical bleeding after a period of CPB is difficult to define because of alterations in several factors that control normal hemostasis. Hemodilution reduces clotting factors and platelets. In addition, platelet function is impaired and a defect in the formation of the platelet plug is thought to be one of the most important causes of bleeding. There is a prolongation of bleeding time during and after CPB. Blood contact with foreign surfaces causes a marked activation of coagulation and secondary activation of the fibrinolytic system. Excessive bleeding may also arise as a result of other causes such as the prior use of

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Table I. *Demographic data and characteristics of the three groups*

Characteristic	*Aprotinin*	*Desmopressin*	*Placebo*
No. of patients	48	50	51
Age (yr)	57 ± 10	58 ± 12	54 ± 12
Sex			
Male	31	33	31
Female	17	17	20
Previous medication (No. of patients)			
Anticoagulants	7	12	11
Antiaggregants	7	7	5
Operative procedure			
CABG	19	19	21
Valve replacement	22	24	19
CABG and valve replacement	1	0	3
Previous cardiac operation	4	4	3
Mitral annuloplasty	2	3	3
Other			2
Duration of operation (min)	178 ± 77	188 ± 41	184 ± 55
Duration of CPB (min)	87 ± 25	89 ± 40	99 ± 36
Duration of ischemia (min)	46 ± 10	46 ± 19	47 ± 21

Age and times are expressed as mean plus or minus standard deviation. No significant differences between groups were observed. *CABG*, Coronary artery bypass grafting.

antiaggregant drugs or deficient heparin neutralization by protamine.[4-10]

In recent years, efforts have been made to design strategies to reduce and control bleeding pharmacologically. Treatments with prostacyclin,[11] antifibrinolytic drugs (aminocaproic acid,[12] tranexamic acid,[13] or aprotinin), or desmopressin[14] have been used for this purpose.

It has been widely demonstrated that aprotinin administration reduces blood loss and blood requirements in patients undergoing CPB.[15-24] Aprotinin is a serine protease inhibitor that efficiently inactivates plasmin and kallikrein,[25] thereby inhibiting fibrinolysis and possibly preserving platelets of activated proteases.[22, 23]

In contrast, the efficacy of desmopressin in CPB varies with the different works reviewed.[14, 26-30] Desmopressin is a synthetic analog of vasopressin. Its administration increases levels of factor VIII and high-molecular-weight multimeric forms of von Willebrand's factor. Its utility has been demonstrated in moderate hemophilia A, in some variants of von Willebrand's disease, and in a heterogeneous group of disorders with prolonged bleeding time.[31-33]

To our knowledge, there have been no comparative studies on the efficacy of aprotinin versus desmopressin in CPB. We therefore performed a double-blind, randomized, prospective study comparing aprotinin, desmopressin, and placebo in an attempt to demonstrate their effectiveness in reducing blood loss and red blood cell requirements in CPB. We also analyzed the influence of each treatment on several hematologic and hemostatic parameters.

Methods

Patients. To be eligible for recruitment, patients had to be older than 18 years and scheduled to undergo either coronary artery bypass grafting, heart valve replacement or annuloplasty, combined valve replacement and coronary artery bypass grafting, or closure of atrial septal defects. Patients requiring emergency operations and those with a history of any bleeding disorder, with a history of allergy, or with previous exposure to aprotinin were not included. Demographic data are summarized in Table I.

Surgical procedures. Anesthetic, surgical, and CPB procedures were done according to the institutional protocols of the Hospital de Sant Pau (Barcelona, Spain) and were similar in all three groups. Patients received chlorazepate (0.5 mg/kg body weight) 2 hours before anesthesia was induced. All patients' conditions were monitored by recording a continuous electrocardiogram, the central venous pressure, the arterial pressure by a radial artery catheter, esophageal and rectal temperatures, hourly urine output, and sequential blood gas measurements. A pulmonary artery catheter was placed in patients with a poor cardiac index (<0.5).

Anesthesia was induced with flunitrazepam (0.02 mg/kg body weight) and fentanyl (10 to 20 μg/kg body weight). Pancuronium bromide (0.1 mg/kg body weight) was used for muscle relaxation. Anesthesia was maintained with successive doses of fentanyl. Isoflurane (0.5% to 1%) was added to the ventilation system when needed.

The CPB device was primed with Ringer's solution, polygeline, and mannitol. Extracorporeal circulation was instituted at 28° C with an output of 2.2 to 2.4 L/m^2 per minute. Perfusion pressure was maintained between 50 and 80 mm Hg. A cardioplegic solution containing mannitol (8.9 gm/L), dextrose (4.5 gm/L), potassium (30 mmol/L), chloride (113 mmol/L), sodium (82 mmol/L), and bicarbonate (20 mmol/L) was injected every 20 minutes into the aortic root.

Anticoagulation was achieved with heparin (300 IU/kg body weight) injected into the right atrium. Successive doses of heparin were given during CPB. Because aprotinin can prolong activated clotting time (Hemochron 401 device, International Technidyne Corp., Edison, N.J.),[23] patients in whom the first activated clotting time measurement was greater than 750 seconds received heparin to

maintain the activated clotting time between 750 and 950 seconds, and in those patients in whom the first activated clotting time measurement was about 400 seconds, activated clotting time was maintained between 400 and 500 seconds. Activated clotting time assays were not done by the participants in the study and the activated clotting time results were not revealed. All groups received heparin in similar dosages. When surgical procedures were finished and CPB was stopped, heparin neutralization with protamine sulfate was achieved by means of an infusion of 1.5 mg/100 IU of heparin administered. Patients were later cared for in the postoperative intensive care unit.

Transfusions were administered according to the following criteria: red blood cells were given when the hemoglobin value was less than 80 gm/L (70 gm/L in CPB period) or when the patient was in shock because of hemorrhage, fresh frozen plasma was given if microvascular bleeding was present with a prothrombin international normalized ratio greater than 1.5 or a fibrinogen level less than 1 gm/L, and platelet concentrates were given in cases of microvascular bleeding and platelet counts less than 60,000/μl.

Study design. The study protocol was approved by the Ethical Clinical Trials Committee. After informed consent was obtained, each patient was independently randomized to either the placebo or drug groups. Expected duration of CPB was taken into account for randomization. Multiple valve replacements, valve replacement plus mitral annuloplasty, bypass grafting of more than two arteries, valve replacement plus coronary artery bypass grafting, and procedures in patients with a history of previous cardiac operation were considered long duration procedures (≥120 minutes of expected CPB time).

On the basis of our previous experience, a sample size of 50 patients in each group was estimated as having 80% power (type II error of 0.2) to demonstrate a statistically significant result if the true reduction of blood loss was 50%, assuming a critical p value of 0.05 (two-sided test). We also assumed a reduction in effective sample size of 20% because of patients eliminated from the study.

Sealed envelopes ensured that only the pharmacist who prepared the encoded infusions knew whether a patient received desmopressin, aprotinin, or placebo. All three compounds were prepared with the same outward appearance. Dosage schedules are shown in Table II.

Patients randomized to the desmopressin group received desmopressin (Ferring Pharmaceuticals, Malmoe, Sweden) as follows: patients with body weight less than 65 kg were given infusions of 20 μg and other patients received 24 μg (corresponding to 0.3 to 0.4 μg/kg body weight). At time 4 (see Table II), desmopressin was infused in 50 ml of saline solution for 20 to 30 minutes, 15 minutes after protamine administration. In other phases, patients received saline solution only.

Aprotinin (Trasylol, Bayer AG, Leverkusen, Germany) was administered in saline solution without additives or preservatives. The following dosage regimen was used in this treatment group: before anesthesia an infusion of 2,000,000 KIU was given over 20 to 30 minutes. A dose of 2,000,000 KIU was added to the priming solution of the heart-lung machine. Aprotinin was administered continuously at 500,000 KIU per hour until the end of the operation (from skin incision to skin closure). At time 4, these patients received saline solution.

Table II. *Dosage schedule*

	Volume administered		
	Placebo group	*Desmopressin group*	*Aprotinin group*
Time 1	PS 200 ml	PS 200 ml	Aprotinin 200 ml
Time 2	PS 200 ml	PS 200 ml	Aprotinin 200 ml
Time 3	PS 50 ml/hr	PS 50 ml/hr	Aprotinin 50 ml/hr
Time 4	PS 50 ml	Desmopressin 50 ml	PS 50 ml

Time 1, Start of anesthesia; *time 2,* drug in fluid prime; *time 3,* skin incision to skin closure; *time 4,* after protamine neutralization; *PS,* physiologic saline solution.

Patients in the placebo group received saline solution during all the stages.

Measurement of blood loss. Intraoperative blood loss was estimated by weighing the gauze sponges and measuring the contents of the reservoir of the suction device. The fluid used for rinsing was subtracted from this amount. Blood drained from chest tubes was recorded at 1, 2, 3, 6, 12, and 24 hours after operation.

The amounts of red blood cell units, fresh frozen plasma, and platelet concentrates infused in each patient in the first 24 hours were also registered.

Laboratory measurements. Blood samples were taken as follows: (1) immediately before operation, (2) after CPB but before the administration of protamine, (3) 15 minutes after protamine administration, (4) 60 minutes after time 4 (see Table II), and (5) 18 to 24 hours after operation. Blood mixed with 0.129 mol/L sodium citrate in a 10:1 proportion was obtained for analysis of plasma factor VIII coagulant activity (FVIIIc), von Willebrand's factor antigen (vWFAg), thrombin-antithrombin (TAT) complexes, and split products of cross-linked fibrin (D-dimer). For measurements of hemoglobin and platelet count, blood was mixed with ethylenediaminetetraacetic acid. Hemoglobin level and platelet counts in whole blood were determined by routine analysis with a Coulter counter (Coulter Electronics, Luton, England). D-dimer and vWFAg levels were measured by an enzyme-linked immunosorbent assay method (Boehringer-Mannheim, Mannheim, Germany). Levels of TAT complexes were determined by sandwich enzyme-linked immunosorbent assay (Behring, Marburg, Germany). FVIIIc was quantified by one-stage clotting assay.

It was possible to determine all these biologic parameters in the five samples from 34 patients in the aprotinin group, 35 patients in the desmopressin group, and 41 patients in the placebo group.

Statistical analysis. Results are expressed as the mean and standard deviations and as the 95% confidence interval (CI). Percentages are expressed with the CI. All relevant differences are shown as the CI of these differences. A p value less than 0.05 was considered significant. Age, body surface area, body weight, and durations of operation and extracorporeal circulation were compared among groups by one-way analysis of variance. Sex, type

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Table III. *Blood loss*

	Blood loss (ml/m² BSA)		
	Aprotinin group	*Desmopressin group*	*Placebo group*
0-1 hr	22 ± 22*	60 ± 45	66 ± 71
1-2 hr	18 ± 16*	51 ± 53	65 ± 62
2-3 hr	15 ± 10*	40 ± 32	48 ± 50
3-6 hr	51 ± 59*	90 ± 72	131 ± 119
6-24 hr	89 ± 80*	159 ± 126	179 ± 154
0-24 hr	195 ± 146*	400 ± 192	489 ± 361
Bypass time <120 min†			
0-6 hr	99 ± 58*	250 ± 155	273 ± 192
6-24 hr	77 ± 40*	162 ± 137	149 ± 72
0-24 hr	176 ± 73*	412 ± 200	422 ± 237
Bypass time ≥120 min†			
0-6 hr	205 ± 193‡	230 ± 152‡	428 ± 373
6-24 hr	184 ± 247‡	120 ± 31‡	270 ± 287
0-24 hr	389 ± 433‡	350 ± 159‡	698 ± 572

Values given as mean plus or minus standard deviation.

*$p < 0.001$ aprotinin versus desmopressin or placebo.

†$p < 0.001$ long duration versus short duration (analysis of variance with two factors).

‡$p < 0.05$ aprotinin or desmopressin versus placebo.

of operation, and previous treatment were compared by a χ^2 test. Primary efficacy analysis was done on the total blood loss during the first 24 hours after operation by an analysis of variance with two factors (treatment and CPB duration, long versus short). A sequential sum of squares method was used because the numbers of patients in the short and long duration groups were very different. An analysis of variance for repeated measures with one factor (treatment) was done to analyze the blood loss profiles at 1, 2, 3, 6, and 24 hours, and CPB duration was used as covariable. Polynomial contrasts were applied within different points to analyze different trends of each treatment. Bonferroni's correction was applied for multiple comparisons. A multiple regression analysis was done to evaluate the relationship between overall blood loss and some clinical or biologic variables.

Differences between percentages of patients receiving transfusion were estimated with a χ^2 method. In patients receiving transfusion, differences in the number of blood units were assessed by analysis of variance with CPB duration as a covariable. A logistic regression model was used to estimate the odds ratio of undergoing transfusion in each treatment group. Age, sex, CPB duration, preoperative hemoglobin value, and preoperative platelet count were included as adjustment variables. The improvement in −2 log likelihood was evaluated to establish the goodness of fit of the model. The evolution of biologic parameters throughout the CPB period was assessed by analysis of variance for repeated measures (treatment as the factor and CPB duration as the covariable). Polynomial contrasts were applied to evaluate profiles between treatments. If no influence of the analyzed factors was observed, a simple analysis of variance for repeated measures was used. D-dimer values were analyzed with the use of a logarithmic transformation.

Results

Clinical setting. The characteristics of the three groups are summarized in Table I. A total of 150 patients were considered for entry, one of whom refused inclusion in the study. The aprotinin group comprised 48 patients, the desmopressin group 50, and the placebo group 51. Age, sex, weight, previous anticoagulant or antiaggregant treatment, and type of operation were similar in the three groups. In patients receiving oral anticoagulation, anticoagulants were stopped and basic hemostatic test results were normal before the operation. Operative and CPB durations were longer in the placebo group but differences were not significant.

Safety. No adverse reactions to the drugs used were noted. Six patients died during the operation: two in the aprotinin group, three in the desmopressin group, and one in the placebo group. All of these were undergoing coronary artery bypass grafting. In every case, death was in relation to a previous severe ischemic cardiomyopathy and no relationship with the treatment regimen was found. Moreover, the patients who died in the desmopressin group died before drug administration. Three patients required reoperation because of bleeding related to the operation (1 in the aprotinin group and 2 in the desmopressin group) and were excluded from data analysis. As for thromboembolic complications, one patient from the placebo group had a femoral embolism on the first day, one patient from the desmopressin group with dilated cardiomyopathy had an ischemic stroke 6 days after operation, and one patient from the aprotinin group had a femoral embolism 6 days after operation.

Blood loss. The results of the study are summarized in Table III. When blood loss was analyzed with regard to type of operation no differences were found. However, blood loss was different in relation to treatment and CPB duration ($p < 0.001$). Intraoperative bleeding showed no differences between groups. When total bleeding was considered (first 24 hours), patients in the aprotinin group bled less than others. They lost 195 ± 146 ml/m² body surface area (BSA) compared with 400 ± 192 ml/m² BSA in the desmopressin group and 489 ± 361 ml/m² BSA in the placebo group (95% CI: difference between desmopressin and aprotinin groups 98 to 312 ml/m² BSA, $p < 0.001$; difference between placebo and aprotinin groups 190 to 398 ml/m² BSA, $p < 0.001$).

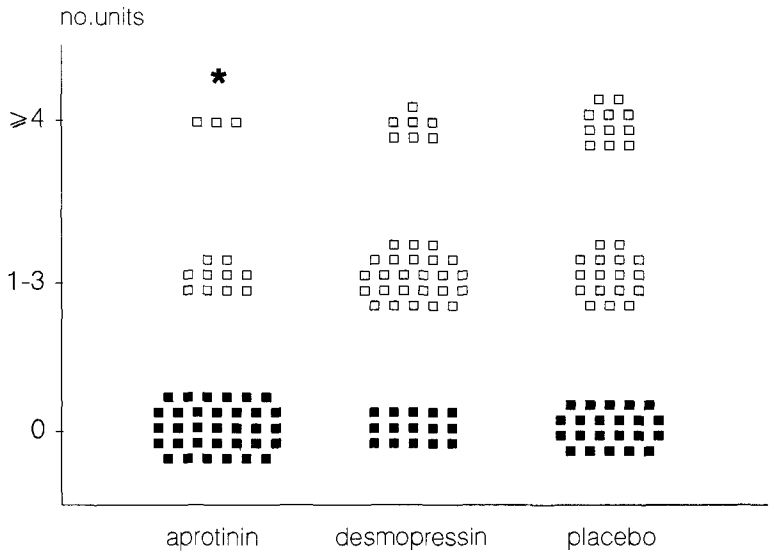

Fig. 1. Red blood cell transfusion requirements by number of units *(no. units)*. Patients in aprotinin group received fewer transfusions than others (*$p < 0.001$). *Bold squares* denote no transfusion.

The increment of blood loss throughout the observation period was linear in all three groups (polynomial contrasts; explained variability for linear trend, 90% in the aprotinin group, 93% in the desmopressin group, 80% in the placebo group).

Hemorrhage was significantly more pronounced in patients with longer CPB times (see Table III). The duration of CPB exceeded 120 minutes in 25 patients (4 with aprotinin, 9 with desmopressin, and 12 with placebo). In this set of patients, total blood loss was 389 ± 433 ml/m^2 BSA with aprotinin, 350 ± 159 ml/m^2 BSA with desmopressin, and 698 ± 572 ml/m^2 BSA with placebo. Differences between the aprotinin and desmopressin groups versus the placebo group were significant (95% CI: difference between placebo and aprotinin groups 29 to 590 ml/m^2 BSA, $p < 0.05$; difference between placebo and desmopressin groups 135 to 563 ml/m^2 BSA, $p < 0.05$).

Blood products requirement. Red blood cell transfusion was required in only 26% (95% CI: 15% to 42%) of patients who received aprotinin compared with 66% (95% CI: 51% to 80%) in the desmopressin group and 56% (95% CI: 41% to 70%) in the placebo group. Differences between aprotinin versus placebo plus desmopressin were significant (95% CI: 51% to 71%; $p < 0.001$). No differences between the placebo and desmopressin groups were observed (see Fig. 1).

The administration of aprotinin protected against the need for red blood cell transfusion as compared with administration of placebo, with a crude odds ratio of 0.31 (95% CI, 0.13 to 0.71; improvement χ^2 14.87, $p = 0.0006$). No effect was seen in the desmopressin group (crude odds ratio 1.46; 95% CI, 0.66 to 3.25). When the model was adjusted for age, sex, initial hemoglobin value and CPB duration (more than 120 minutes, less than 120 minutes), patients with long CPB procedures had a higher risk of receiving red blood cell units (adjusted odds ratio 12.32; 95% CI, 2.95 to 51.21). The patients in whom initial hemoglobin levels were higher had a lower risk of transfusion (adjusted odds ratio 0.36; 95% CI, 0.17 to 0.75; improvement χ^2 41.87, $p < 0.0001$).

Requirements expressed as mean (range) of red blood cell units were 0.7 (0 to 6) units in the aprotinin group, 1.6 (0 to 6) in the desmopressin group, and 1.8 (0 to 8) in the placebo group. If we consider only patients who received transfusion, no significant differences among groups were observed in relation to the number of red blood cell units transfused (2.54 ± 1.81 in the aprotinin group, 2.59 ± 1.54 in the desmopressin group, and 3.25 ± 1.96 in the placebo group). In long duration procedures, differences among groups were also not found (aprotinin group 2.25 ± 1.89 units, desmopressin group 2.28 ± 1.50 units, and placebo group 4.36 ± 2.34 units). Patients with short procedures received 46% fewer transfusions (95% CI, 31% to 62%) than others.

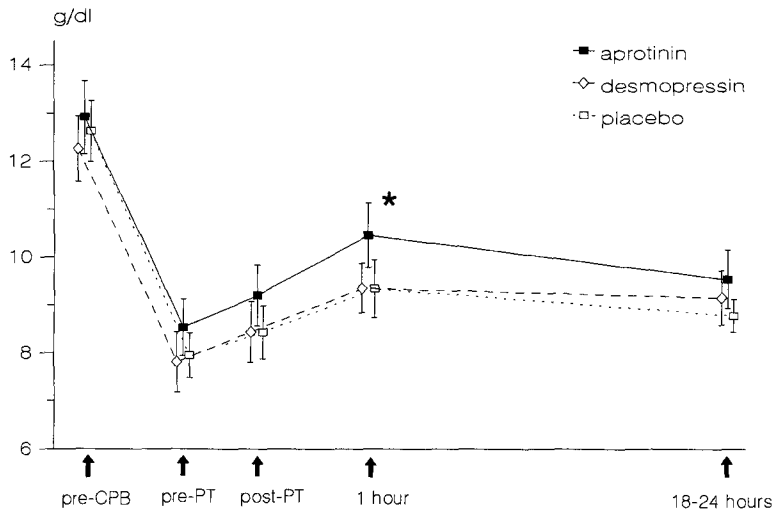

Fig. 2. Evolution of hemoglobin levels throughout observation period. All groups showed decrease caused by hemodilution, but at end of CPB (fourth determination), hemoglobin level was higher in patients who received aprotinin ($^*p < 0.05$). At 24 hours, there were no differences between groups, but desmopressin and placebo groups received more red blood cell units. *PT,* Protamine.

Five patients (1 from the placebo group and 4 from the desmopressin group) needed fresh frozen plasma transfusion, and platelet concentrates were given to nine patients (1 from the aprotinin group, 3 from the desmopressin group, and 5 from the placebo group).

Hematologic parameters. All groups had similar presurgical levels of hemoglobin. A decrease was observed during CPB mainly because of hemodilution and was followed by a slight rise. The hemoglobin level at the end of CPB was significantly higher in patients who received aprotinin. Nevertheless, no difference was observed in the hemoglobin measurement at 24 hours. This could be explained by the fact that the aprotinin group received fewer transfusions than the other groups (Fig. 2). The platelet count decreased in all patients during CPB and no differences among groups were observed. FVIIIc and vWFAg levels also decreased in the extracorporeal period probably in relation to hemodilution (see Table IV). Subsequently, vWFAg levels increased with respect to the initial values. No differences were noted in these two factors in patients treated with desmopressin. Measurements of TAT complexes were not statistically different and a dramatic increase was observed in all patients throughout the CPB period (see Table IV).

As for D-dimer, the evolution was clearly different among groups (see Fig. 3 and Table IV). Patients receiving desmopressin or placebo showed a marked increase in D-dimer levels during CPB (explained variability for quadratic trend, 80%). In contrast, patients treated with aprotinin showed a slight rise in D-dimer levels at the end of CPB (explained variability for linear trend, 50%; quadratic trend, 43%). Differences between the aprotinin group and the desmopressin or placebo groups were significant. A regression multiple analysis with the following variables was applied: all biologic parameters at the end of CPB, CPB duration, type of treatment, and overall bleeding as dependent variable. A multiple regression coefficient of 0.61 ($F = 17.36, p < 0.0001$) was obtained. Only D-dimer level and the use of aprotinin were significant. The equation of this model was as follows: overall bleeding = 382.7 + 0.013 (D-dimer) − 242.8 aprotinin, where overall bleeding units are milliliters per meter squared, D-dimer units micrograms per liter, and aprotinin can be 1 (if used) or 0 (if not used). Fig. 4 represents the linear correlation between overall blood loss and the level of D-dimer at the end of CPB in the desmopressin and placebo groups, but not in the aprotinin group.

Discussion

The management of bleeding remains a major challenge in patients undergoing CPB procedures. Different pharmacologic strategies have recently been the focus of attention given that their use is potentially less hazardous than the administration of blood products. Two drugs have demonstrated their

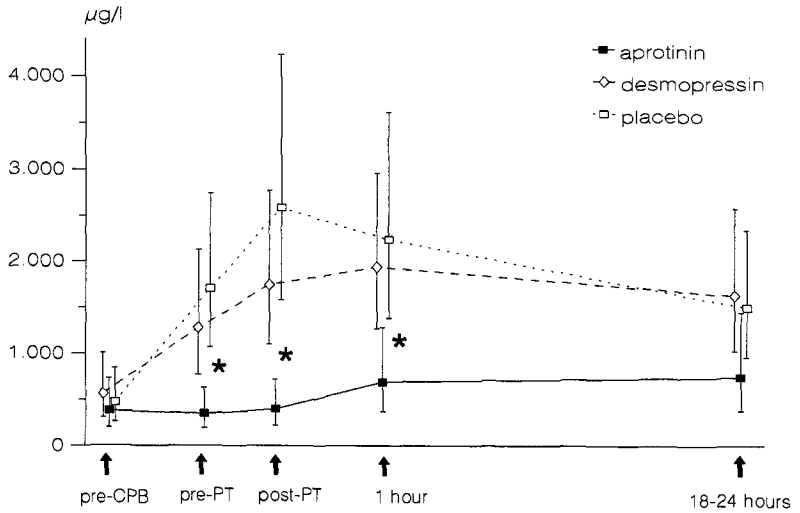

Fig. 3. D-dimer levels markedly increased during CPB in desmopressin and placebo groups, but not in aprotinin group (*$p < 0.05$). D-dimer level is expressed as geometric means. *PT,* Protamine.

Table IV. *Biological parameters in the three treatment groups*

	Groups		
	Aprotinin (n = 34)	*Desmopressin (n = 35)*	*Placebo (n = 41)*
D-dimer (μg/L)			
Before operation	1852 ± 876	1545 ± 469	2526 ± 1128
Before protamine	1646 ± 795	3172 ± 909*	6014 ± 2291*
After protamine (15 min)	1957 ± 985	3834 ± 963*	7601 ± 2557*
After protamine (75 min)	4205 ± 2344	3877 ± 1296*	6809 ± 2365*
18-24 hr	4714 ± 2999	4064 ± 1087	4927 ± 2156
TAT complexes (μg/L)			
Before operation	13.3 ± 13.9	19.2 ± 23.1	22.9 ± 26.1
Before protamine	55.9 ± 43.9	95.3 ± 77.3	76.7 ± 49.8
After protamine (15 min)	85.9 ± 51.5	122.4 ± 120.7	92.9 ± 48.3
After protamine (75 min)	56.7 ± 48.8	68.2 ± 61.8	59.1 ± 28.8
18-24 hr	24.2 ± 28.2	29.0 ± 44.9	18.6 ± 11.5
FVIIIc (%)			
Before operation	117 ± 68	115 ± 46	121 ± 55
Before protamine	17 ± 17	22 ± 35	12 ± 11
After protamine (15 min)	76 ± 33	72 ± 37	68 ± 30
After protamine (75 min)	106 ± 46	101 ± 42	92 ± 48
18-24 hr	124 ± 52	119 ± 40	133 ± 42
vWFAg (%)			
Before operation	145 ± 73	154 ± 77	151 ± 67
Before protamine	126 ± 71	126 ± 65	142 ± 73
After protamine (15 min)	152 ± 70	148 ± 76	164 ± 69
After protamine (75 min)	184 ± 84	181 ± 70	177 ± 79
18-24 hr	206 ± 98	185 ± 77	198 ± 78

Values given as mean plus or minus standard deviation except for D-dimer values, which are given as mean plus or minus standard error. TAT, vWFAg, and FVIIIc values showed no differences among groups. D-dimer level was higher in the placebo and desmopressin groups.
*$p < 0.05$.

possible usefulness: aprotinin and desmopressin. The efficacy of desmopressin is still controversial. Salzman[14] and Czer[26] and their colleagues found a beneficial effect in patients with a long duration of CPB and severe bleeding. By contrast, other authors demonstrated no reduction in bleeding.[28, 29] The different conclusions could possibly be explained by the fact that the populations were not comparable.

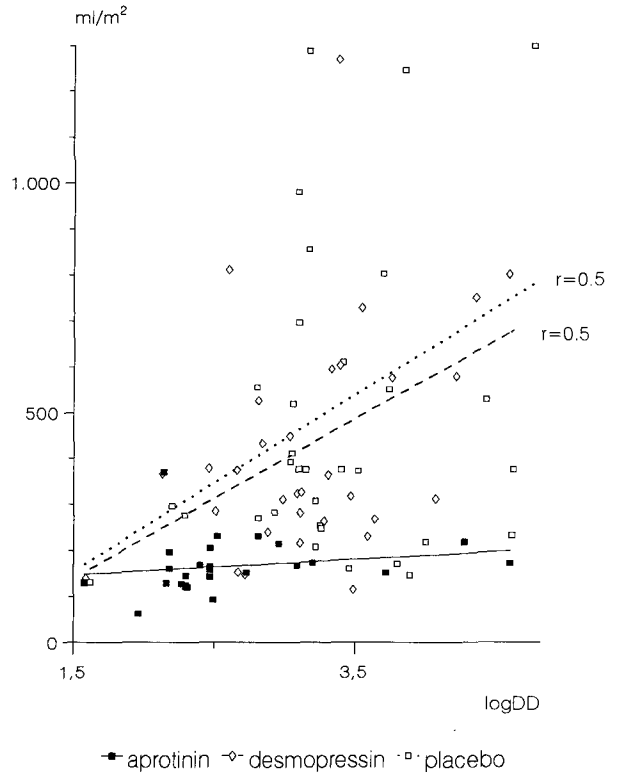

Fig. 4. Correlation between overall blood loss (in milliliters per meter squared) and D-dimer measurement after protamine neutralization in desmopressin and placebo groups ($p < 0.01$). This correlation did not exist in aprotinin groups. *logDD,* Logarithm of D-dimer.

On the other hand, in our own clinical experience some patients showed a good response to desmopressin infusion. For these reasons we decided to include in our study a treatment group receiving desmopressin. Moreover, aprotinin has proved to be beneficial in reducing blood loss in operations done with CPB,[15-24] but to our knowledge no comparative study of aprotinin and desmopressin has been done.

Bleeding. The overall analysis of blood loss revealed a beneficial effect of aprotinin in operations done with CPB. Its use reduced bleeding roughly by half compared with results with desmopressin or placebo. No overall differences were noted between the placebo and desmopressin groups. As for CPB duration, patients with long CPB times (longer than 120 minutes) had more bleeding. Eighteen patients initially randomized as requiring a long duration of CPB (10 in aprotinin group, 5 in desmopressin group, and 3 in placebo group) had shorter CPB times. There were fewer patients with a long duration of CPB in the aprotinin group than in the other groups. A possible advantage of aprotinin in this reduction could not be demonstrated. Although the group of patients with CPB times exceeding 120 minutes was small, aprotinin and desmopressin seemed to be more effective than placebo in preventing bleeding. One recent report found no advantage with desmopressin in operations done with CPB,[30] but desmopressin was administered only if significant postoperative bleeding was present and the authors did not distinguish between short and long CPB durations. A recent report supports desmopressin as being safe and useful in reducing blood loss and transfusion requirements in patients with excessive bleeding after operations with CPB.[34] We found no differences between groups with respect to previous intake of antiaggregant or anticoagulant drugs and no influence was confirmed in bleeding complications.

Blood product requirements. Reduction of blood loss in patients treated with aprotinin was followed by a saving in blood products. Only a quarter of these patients needed red blood cell units. In contrast, more than half the patients in other groups received transfusions. Although the level of hemoglobin at the end of CPB was slightly higher in the aprotinin group, it was similar in all groups at 24 hours after the operation. This finding can be easily explained by a higher rate of transfusion needs in the desmopressin and placebo groups. When CPB duration was longer than 120 minutes, nearly all the patients required transfusion. Patients treated with aprotinin or desmopressin received a smaller number of red blood cell units than patients in the placebo group, but the differences were not significant. No comparisons could be made with respect to other types of blood products because their use was minimal. Nevertheless, except for one patient in the aprotinin group, all platelet or plasma transfusions were given to patients treated with desmopressin or placebo.

Safety. No hypersensitive or other adverse reactions related to the administration of desmopressin or aprotinin were observed. Six patients died during the operation (2 in the aprotinin group, 3 in the desmopressin group, and 1 in the placebo group). All were patients requiring coronary artery bypass grafting. Death was due to surgical or hemodynamic complications related to a previous severe ischemic cardiomyopathy, and no relationship with the treatment regimen was found. It should be pointed out

that the three patients who died in the desmopressin group died before the drug was administered. In coronary artery bypass grafting we did not perform an angiographic evaluation of bypass patency after the operation, although no differences between groups were observed for frequencies of myocardial infarction or unstable angina. Moreover, the clinical assessment of patients' conditions 1 year after the operation disclosed no differences with respect to the prevalence of recurrent angina or myocardial infarction among groups. Three late thromboembolic events were observed, one in each group. Relationship with the drug used was unlikely. A recent analysis of studies that compared hemostatic efficacy of desmopressin versus placebo concluded that desmopressin does not increase the prevalence of thrombosis.[35]

Hematologic measurements. It is widely known that desmopressin produces an increase in plasma levels of FVIIIc and vWFAg,[32] which proceed from endothelial cells. In common with other authors[28] we did not find any differences between groups in relation to FVIIIc and vWFAg levels. All groups showed a similar increase in both factors after CPB. The known effect of aprotinin in hemostasis is caused by its ability to inhibit plasmin and kallikrein. Kallikrein plays a role in the activation of the intrinsic pathway of blood coagulation. Recently, this pathway of clotting activation has been considered to be of less importance.[36] Kallikrein also participates in the intrinsic fibrinolytic activation pathway. However, the advantage of aprotinin probably springs from its capacity to inhibit plasmin.[25] In operations with CPB there is a marked activation of coagulation caused by tissue injury, platelet destruction, and contact with foreign surfaces. Coagulation activation can be estimated by levels of TAT complex, a thrombin generation marker.[37] No differences in TAT complex levels were found between groups. This could indicate that clotting activation was similar in the three groups. D-dimer is a fibrinolytic marker because it is formed by the action of plasmin over cross-linked fibrin. In our study, the patients who received aprotinin showed no significant increase in D-dimer levels, whereas patients who received desmopressin and placebo underwent a dramatic rise in D-dimer levels. Patients receiving aprotinin thus had an efficient inhibition of fibrinolysis. CPB-associated hyperfibrinolysis has been positively correlated with bleeding.[38] We found a correlation between overall blood loss and D-dimer level in patients treated with desmopressin or placebo, but not in those in the aprotinin group. In the aprotinin group, there was a poor fibrinolytic response caused by plasmin inhibition. Moreover, the multiple regression model shows that the use of aprotinin is clearly related to a reduction of blood loss.

Conclusion. We can conclude that the administration of aprotinin to patients undergoing operation with CPB significantly reduces blood loss and blood cell requirements. Aprotinin produces a marked inhibition of fibrinolysis in vivo, which may be important in explaining its positive effect on reducing blood loss.

Although the administration of desmopressin did not show any benefit in overall bleeding, it may be useful for patients who have long duration procedures, because it is administered after the end of CPB. We would like to emphasize that in our experience aprotinin treatment is safe and should be used in all patients undergoing CPB provided they have no history of aprotinin allergy. Given that the mechanisms of action of desmopressin and aprotinin are different, further studies are necessary to test the possible synergic benefits of aprotinin together with desmopressin in operations done with CPB.

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