

Does desmopressin acetate reduce blood loss after surgery in patients on cardiopulmonary bypass?

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ABSTRACT It has been suggested that desmopressin acetate (DDAVP) administration reduces blood loss after cardiac surgery. We have investigated the effect of DDAVP administration in a double-blind, randomized, prospective trial including 100 patients placed on cardiopulmonary bypass during surgery. Fifty patients received 0.3 µg/kg DDAVP and 50 patients received a placebo administered in a 50 ml saline solution over 15 min when cardiopulmonary bypass had been concluded. Results showed no significant differences either in total blood loss per square meter (458 ± 206 ml in the DDAVP group vs 536 ± 304 ml in the placebo group) or in necessity for red cell transfusions (1642 ± 705 ml in the DDAVP group vs 1574 ± 645 ml in the placebo group) in the first 72 hr after surgery. Only intraoperative blood loss per square meter was significantly lower ($p < .02$) in the DDAVP group (131 ± 106 ml) as compared with the placebo group (193 ± 137 ml). The prolongation of bleeding time and the decrease of factor VIII:C and factor VIII:von Willebrand factor 90 min after treatment were significantly lower ($p < .001$) in the DDAVP group as compared with the placebo group. We conclude that the administration of DDAVP in patients placed on cardiopulmonary bypass during surgery does not reduce total blood loss and is only effective in reducing intraoperative bleeding.

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PATIENTS placed on cardiopulmonary bypass (CPB) for open heart surgery have an increased susceptibility to postoperative bleeding.¹ Reoperation for bleeding control is sometimes necessary and occasionally life-threatening hemorrhaging occurs during the postoperative period. The majority of patients bleed primarily from the operative site. However, in some patients, diffuse systemic bleeding^{2,3} suggests an acute acquired hemostatic defect. The basic pathophysiology of altered hemostasis associated with CPB remains confusing. The abnormalities most frequently found include heparin and protamine excess, heparin rebound, low platelet count, abnormal platelet function, low fibrinogen, primary fibrinolysis, and disseminated intravascular coagulation.⁴⁻¹⁶

Since a significant platelet function defect may be the primary cause of hemorrhage, the use of platelet concentrates and prostacyclin has been suggested.^{2,17,18} A defect in ristocetin-induced platelet aggregation has been described in these patients,² suggesting

a role for von Willebrand factor in the hemostatic defect.¹⁹ Recently, Salzman et al.²⁰ showed that desmopressin acetate (DDAVP) reduced postoperative blood loss in patients undergoing CPB. They suggested that the elevation in the plasma concentration of von Willebrand factor induced by DDAVP, possibly in association with a change in the distribution of von Willebrand factor multimers, was the most likely explanation for the beneficial effect of the drug in CPB. However, it has been argued that the good results found by Salzman et al. may be related to the high postoperative blood loss reported in their patients.^{21,22}

DDAVP is a synthetic analog of the neurohypophyseal nonapeptide arginine vasopressin. It is known that this hormone causes the appearance of larger von Willebrand's factor multimers in addition to increased concentrations of factor VIII:von Willebrand factor and factor VIII:C and thus a role for DDAVP has been indicated in patients with mild hemophilia or von Willebrand's disease.²³ DDAVP has also been shown to shorten the bleeding time in other conditions, including uremia, chronic liver disease, and aspirin ingestion.²⁴⁻²⁶

In the present study we evaluated the effectiveness of intraoperative DDAVP in the reduction of blood loss during the postoperative period in a double-blind,

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randomized, prospective trial involving 100 patients placed on CPB during surgery.

Methods

Study population. To be eligible for recruitment, patients had to satisfy the following inclusion criteria: age over 18 years and valvular heart disease or atrial septal defects. Patients were excluded for the following reasons: emergency surgery, known hemostatic defect, uncontrolled hypertension, and renal insufficiency. Patients undergoing coronary artery bypass grafting were also excluded on the basis of a possible hypercoagulable state secondary to an increase of von Willebrand factor due to administration of DDAVP.

Study design. The protocol was approved by our hospital's Clinical Assays Committee. After obtaining informed consent, a prospective double-blind, randomized trial involving 100 patients was begun. Patients were randomly assigned to one of the following groups: (1) Fifty patients received DDAVP, 0.3 µg/kg body weight, maximum 20 µg (kindly supplied by Ferring Pharmaceuticals, Malmö, Sweden). (2) Fifty patients received a placebo similar in appearance to the drug.

On completion of CPB and immediately after administration of protamine, treatment was administered intravenously in a 50 ml solution for 15 min.

Methods of data analysis. Blood samples were obtained before operation, immediately before treatment was started, 90 min after administration of treatment, and 24 hr postoperatively.

The following measurements were obtained in all samples. Hematocrit, hemoglobin, and platelet count were measured with a Coulter S Plus II. Factor VIII:C was determined as described by Hardisty and McPherson.²⁷ Factor VIII: von Willebrand factor was measured by an ELISA method (Boehringer Mannheim, Mannheim, W. Germany). Bleeding time was determined by the Simplate II technique (General Diagnostics, New Jersey)²⁸ before operation and 90 min after administration of treatment.

Intraoperative blood loss starting at the time of treatment administration and postoperative blood loss in the first 72 hr were measured by weighing sponges and measurement of drainages. Red cell transfusions in the first 3 postoperative days were recorded. Blood pressure and urine output in the first 24 hr were measured.

Statistical methods. Results are expressed as the mean ± SD. Student's t test was used to compare mean values, and Student's t test for paired observations was used to compare the mean value of the same variable at different times. Comparison of proportions was performed according to Fisher's exact test.

Results

One hundred eligible patients consented to participate in this trial. The baseline characteristics, the main diagnoses, and types of surgery are listed in table 1. There were no significant differences with regard to any of the characteristics analyzed between the two groups of patients.

Determinations of hematocrit, hemoglobin, platelet count, factor VIII:C, and factor VIII: von Willebrand factor before surgery, immediately before and 90 min after administration of treatment, and 24 hr postoperatively are indicated in figure 1. Bleeding time before surgery and 90 min after therapy is also shown. Preop-

TABLE 1
Characteristics of the two groups of patients

Characteristic	DDAVP	Placebo
Age (years)	55 ± 13	53 ± 12
Sex (male/female)	19/31	25/25
Body surface area (m ²)	1.7 ± 0.1	1.7 ± 0.1
Principal diagnosis		
Mitral stenosis	9	9
Mitral regurgitation	4	2
Double mitral lesion	10	13
Aortic stenosis	4	6
Aortic regurgitation	6	0
Double aortic lesion	6	12
Atrial septal defect	4	1
Double mitral and double aortic lesion	3	3
Mitral and aortic regurgitation	0	1
Double mitral and double tricuspid lesion	1	0
Double mitral lesion and tricuspid regurgitation	2	0
Mitral and tricuspid regurgitation	1	0
Mitral stenosis and tricuspid regurgitation	0	1
Double mitral and aortic lesion plus tricuspid regurgitation	0	2
Operative procedure		
Mitral valve replacement	19	16
Mitral commissurotomy	4	6
Mitral anuloplasty	0	2
Aortic valve replacement	16	18
Mitral and aortic valve replacement	3	4
Mitral valve replacement and tricuspid anuloplasty	4	1
Mitral and aortic valve replacement plus tricuspid anuloplasty	0	2
Closure of atrial septal defect	4	1
Duration of extracorporeal circulation (min)	93 ± 43	94 ± 40

No significant differences between groups were observed.

eratively, the mean values were similar in both groups, with no significant differences. There was a significant decline ($p < .0001$) in hematocrit and hemoglobin in blood samples obtained immediately before treatment compared with the basal value, and this was similar in both groups. Both variables recovered 24 hr after surgery. A significant decrease ($p < .0001$) in platelet count compared with the basal value, without changes during the first 24 hr of the postoperative period, was observed in both groups.

In the placebo group there was a significant decrease in factor VIII:C ($p < .001$) immediately before treatment (0.94 ± 0.06 U/ml) compared with the basal value (1.29 ± 0.08 U/ml). A similar decline was observed in the blood sample obtained 90 min after treatment (0.96 ± 0.07 U/ml); the value returned to normal 24 hr after surgery (1.16 ± 0.06 U/ml).

In the DDAVP group there was a decrease in factor VIII:C similar to that observed in the placebo group

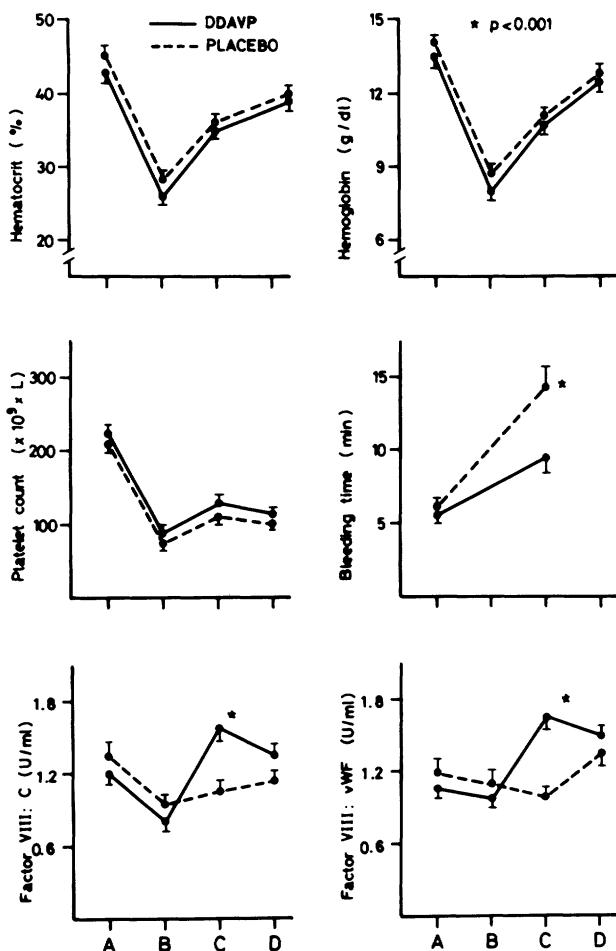


FIGURE 1. Evolution of hematocrit, hemoglobin, platelet count, bleeding time, factor VIII:C, and factor VIII:vWF in blood samples obtained before operation (A), immediately before (B) and 90 min after (C) treatment, and 24 hr postoperatively (D) in patients treated with DDAVP (—) or placebo (---). The mean \pm SEM is reported. * p < .001 as compared with the control group.

immediately before infusion (0.83 ± 0.06 U/ml); the differences were significant ($p < .001$) compared with the basal value (1.23 ± 0.07 U/ml). However, 90 min after therapy there was a marked increase in factor VIII:C (1.62 ± 0.12 U/ml), with a significant difference compared with the basal value ($p < .005$) and with the same value in the placebo group ($p < .001$). As shown in figure 1, modifications similar to those described for factor VIII:C were observed for factor VIII:von Willebrand factor.

Bleeding time showed a marked prolongation in the placebo group 90 min after administration of treatment (13.8 ± 1.1 min) compared with the basal value (5.9 ± 0.3 min; $p < .001$). DDAVP therapy partially corrected the prolongation of bleeding time at 90 min of infusion (9.4 ± 0.7 vs 5.6 ± 0.4 min before surgery) and there was a significant difference compared with the value for the placebo group ($p < .001$).

Results of blood loss and red cell transfusions are shown in table 2. Total blood loss per square meter in the first 72 hr was 536 ± 304 ml in the placebo group and 458 ± 206 ml in the DDAVP group; this difference was not significant. Therefore, no differences in blood loss in the first 24 hr were observed between groups. Only intraoperative blood loss was significantly lower ($p < .02$) in the DDAVP group (131 ± 106 ml) than in the placebo group (193 ± 137 ml). One patient in the placebo group required surgical reoperation to control hemorrhaging. The volume of red cell transfused in the first 3 days was similar in both groups.

No correlation between bleeding time, factor VIII:C, and factor VIII:von Willebrand factor and total blood loss was observed in the samples obtained preoperatively and 90 min after treatment. In the sample obtained 90 min after administration of treatment a significant correlation between factor VIII:C and intraoperative blood loss was found ($r = -.36$, $p < .001$). However, no correlation of intraoperative blood loss with bleeding time and factor VIII:von Willebrand factor could be demonstrated in this sample.

As shown in table 2, DDAVP therapy provoked no complications either in regard to blood pressure or urine output. No deaths or severe complications occurred intraoperatively or on the first 3 postoperative days in any patients included in the study.

Discussion

Patients undergoing cardiac surgery under CPB are known to have increased blood loss intra- and postoperatively. Excessive hemorrhaging occasionally requires reoperation. Recently Salzman et al., in a dou-

TABLE 2
Results of the study

	DDAVP	Placebo
Blood loss/m ² (ml)		
Intraoperative	131 ± 106	193 ± 137^a
0–24 hr	249 ± 144	253 ± 224
24–72 hr	78 ± 58	89 ± 89
Total	458 ± 206	536 ± 304
Red cell transfusions (ml)		
0–24 hr	1366 ± 561	1352 ± 418
24–72 hr	276 ± 494	222 ± 430
Total	1642 ± 705	1574 ± 645
Blood pressure (mm Hg)		
High	134 ± 29	122 ± 38
Low	75 ± 16	73 ± 12
Urinary output in 24 hr (ml)	2437 ± 857	2329 ± 616

^a $p < .02$.

ble-blind, randomized trial, concluded that DDAVP effectively reduced blood loss and transfusion requirements in these patients,²⁰ thus confirming results of a previous clinical nonrandomized trial carried out by Czer *et al.*²⁹ However, Salzman's study has been criticized because his patients had suffered excessive blood loss.²²

The objective of our study was to confirm the efficacy of DDAVP in reducing blood loss and transfusion requirements in patients undergoing surgery under CPB in a double-blind, randomized, prospective trial involving 100 patients. In our study the administration of DDAVP significantly reduced the postoperative prolongation of bleeding time and avoided the decrease in plasmatic levels of factor VIII:C and factor VIII:von Willebrand factor and even increased these levels. Similar results with the same drug have been obtained under other clinical conditions^{23–26} and are in agreement with Salzman's data.²⁰

In spite of these reported analytic changes we cannot confirm that DDAVP reduces total blood loss and transfusion requirements, although it was observed to significantly reduce intraoperative blood loss.

The characteristics of the patients included in our study were similar with respect to age, sex, diagnosis, and operative procedure to those in Salzman's study, except that in his previous study, a small patient group with coronary artery disease, known to have high perioperative bleeding complications, was included and the duration of extracorporeal circulation was longer. Thus, it seems unlikely that differences in characteristics of the patients in the studies are responsible for the disparate findings.

Unlike Salzman's study, which measured total blood loss, we evaluated the blood loss in relation to body surface, which in our experience is a more exact and objective determination. On the other hand, blood loss observed in both groups was considerably less in our study, which supports Allen's criticism comment.²²

In Salzman's study a correlation between the preoperative plasma level of factor VIII:von Willebrand factor and subsequent blood loss was shown. We found no significant correlation of blood loss with preoperative factor VIII:C, factor VIII:von Willebrand factor, or bleeding time. The significant correlation between intraoperative blood loss and factor VIII:C levels 90 min after treatment suggests that this reduction might be related to an increase in factor VIII:C induced by DDAVP. In spite of the lack of demonstrable correlation between intraoperative blood loss and factor VIII:von Willebrand factor in the sample ob-

tained 90 min after treatment, a reduction in such a loss due to a change in the distribution of von Willebrand factor multimers secondary to DDAVP administration cannot be excluded.

We conclude that the administration of DDAVP in patients placed on CPB for surgery for valvular heart disease or atrial septal defect does not reduce total blood loss and is only effective in reducing intraoperative bleeding. Taking into account its lack of side effects, we would recommend use of this drug in patients with excessive intraoperative hemorrhage.

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Retraction

Spinelli W, Kline RP, Meiri H, Robinson RB, Rosen MR: Effect of SC-72-14 on delayed afterdepolarizations and α Nai in ouabain-superfused Purkinje fiber. *74(suppl II)*: II-420, 1986 (abst)

The authors have requested retraction of the above abstract. Results may have been distorted by antibody that was accidentally contaminated in Dr. Meiri's laboratory and subsequently distributed.