# USE OF DESMOPRESSIN IN CARDIAC VALVE SURGERY

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*During the first 24 hours following cardiac surgery, a tendency to bleeding is commonly observed. This situation often requires transfusion of blood or blood products. Desmopressin (DDAVP), a synthetic analoque of the antidiuretic hormone L-arginine vasopressin, may be helpful in lessening of nonsurgical postoperative bleeding following open heart surgery.*

*Two groups of patients undergoing cardiac valve surgery, each consisting of 15 patients were studied. DDAVP was administered to the first group, and the second group was accepted as the control group.*

*Preoperative and early postoperative (pre DDAVP, at 1 hr, 4h, 24 h after DDAVP) values of hemoglobin, hematocrit, platelet counts, bleeding time, prothrombin time, factor VIII procoagulant (F VIII:C), fibrinogen and fibrinogen-fibrin degradation products were measured. Serum sodium, potassium, urea and creatinine levels were recorded. The postoperative blood loss within the first 24 hours was assessed by the amount of mediastinal drainage. The amount of blood, blood products transfused was recorded.*

*There were no significant differences in age, sex, diagnosis, preoperative hematocrit, platelet count, bleeding time, prothrombin time, operative procedure, or preoperative the drugs.*

*Postoperative mediastinal tube drainage was 11.7±7 ml/h (283 ±169 ml/24 hrs) in the DDAVP group, and 24.5±20.8 ml/h (590±500ml/24 hrs) in the control group ($p< 0.05$).*

*Overall blood product utilization was significantly less in the DDAVP group (1 unit/patient, compared with 2.2±1.4 units/patient) ($p< 0.05$). Only 1 patient in the DDAVP group required reoperation who had a surgical bleeding.*

*There was no significant change in bleeding time after desmopressin administration. Fibrinogen levels and FVIII:C activity increased significantly ($p< 0.001$). The mean platelet count remained unchanged after DDAVP. Serum creatinine and urea levels increased slightly but they returned back to normal levels. Administration of DDAVP reduced transfusion requirements, and blood loss in patients with severe platelet dysfunction and bleeding after cardiopulmonary bypass.*

*Key words: Desmopressin (DDAVP), bleeding, cardiac valve surgery.*

During the first 24 hours after cardiac surgery, a tendency of bleeding is commonly observed. This often requires transfusion of blood or blood products. Many factors have been implicated in postoperative bleeding, including surgical causes, dilutional coagulopathy, thrombocytopenia, qualitative platelet defects, inadequate reversal of heparin, anticoagulation, and excessive administration of protamin sulfate.

Desmopressin (1-desamino-8-D-arginine vasopressin) (DDAVP) is a synthetic analogue of the antidiuretic hormone-L-arginine vasopressin. Because it can raise circulating levels of factor VIII, coagulant activity (FVIII), and von Willebrand factor, and shortens the prolonged bleeding time, DDAVP is established as a nontransfusional form of treatment for mild and moderate hemophilia and von Willebrand disease. By increasing plasma levels of von Willebrand factor, DDAVP shortens bleeding time, improves hemostasis, and reduces postoperative blood loss in patients with a variety of platelet disorders[1].

It is believed that DDAVP might have a role in the treatment of mediastinal bleeding when associated with severe platelet dysfunction after cardiopulmonary bypass. The purpose of the study was to determine whether, in this setting, DDAVP reduces transfusion requirements, blood loss and bleeding time.

## Material and Methods

Two groups of patients undergoing cardiac valve surgery, each consisting of 15 patients were studied. DDAVP was administered to group I, and group II was the control group. Preoperative clinical and laboratory characteristics are presented in Table I and II. All of the operations were performed under standart cardiopulmonary techniques. Anesthetic premedication was done with diazepam, and induction with fentanyl citrate and pancronium bromide. A roller or centrifugal pump and membrane oxygenators were used in every case. Moderate systemic hypothermia was applied with a hemodilution rate of 25% hematocrite. Myocardial preservation was provided either with systemic and topical hypothermia using intermittent cold blood and crystalloid (St Thomas II) cardioplegia, or continuous normothermic antegrade - retrograde blood cardioplegia at a body temperature of 37°C. Because of the relatively short durations of aortic cross clamp and total perfusion periods, the type of myocardial preservation had no adverse influence on the total post operative drainage.

In 27 patients, valve replacement was performed utilizing St. Jude Medical (n=26), Duromedics (n=5) Bjork-Shiley (n=1) or Sorin (n=1) prosthetic valves.

After termination of cardiopulmonary bypass, heparin was neutrilized with protamin sulfate according to activated clotting time. DDAVP infusion was started after neutralization and lasted for 30 minutes.

The infusion consisted of DDAVP (0.3 μg per kilogram of body weight) in 50 ml of physiologic saline or (in the control group) physiologic saline alone.

Blood samples were obtained through a flushed arterial catheter at the following times: immediately before operation, after the administration of protamin sulfate but before administration of DDAVP, and at 1, 4 and 24 hours after its administration.

In all patients preoperative and early postoperative measurement of hemoglobin, hematocrit levels, platelet counts, bleeding time, prothrombin time, factor VIII, fibrinogen and fibrinogen-fibrin degradation products were measured.

The concentrations of serum sodium, potassium, urea and creatinine were recorded. The postoperative blood loss within the first 24 hours was assessed by the amount of mediastinal blood drainage.

The amount of cell products and colloid transfusion was recorded. One unit of packed red cells was considered to contain 400 ml and one unit of plasma to contain 200 ml.

## Results

Preoperative and postoperative variables of patients are shown in Table I and II. There were no significant differences in age, sex,

**Table I:** Preoperative and operative characteristics of the two groups.

| Characteristics | DDAVP | Control |
|---|---|---|
| No. of patients | 15 | 15 |
| Valvular lesion | | |
| Mitral stenosis (MS) | 7 | 3 |
| Mitral regurgitation (MI) | — | 1 |
| Aortic stenosis (AS) | — | — |
| Aortic regurgitation (AI) | — | 2 |
| MS+MI | 5 | 8 |
| MS+MI+AS+AI | 3 | 1 |
| Sex | | |
| Male | 7 | 6 |
| Female | 8 | 9 |
| Age | | |
| <30 | 1 | 1 |
| 31-40 | 8 | 6 |
| 41-50 | 4 | 8 |
| 51-60 | 1 | — |
| 60-+ | 1 | — |
| Operative procedure | | |
| AVR | — | 2 |
| MVR | 10 | 8 |
| Aortic and mitral (AVR+MVR) | 2 | 3 |
| AVR-MVR-tricuspit annuloplasty | 1 | — |
| MVR-tricuspit annuloplasty | 1 | — |
| OMV-tricuspit annuloplasty | 1 | — |
| OMV | — | 1 |
| Mitral ring annuloplasty | — | 1 |

DDAVP: Desmopressin
AVR: Aortic valve replacement
MVR: Mitral valve replacement
OMV: Open mitral valvotomy

diagnosis, preoperative hematocrit levels, platelet counts, bleeding time, and prothrombin time, operative procedure or preoperative drugs.

**Postoperative bleeding, blood product utilization and reoperation (Table III).** During postoperative 24 hours of observation, mean mediastinal dramage was 11.7±7 ml/h (283 ±169 ml/24 h) in the DDAVP group and 24.5±20.8 ml/h (590±500 ml/24 h) in the control group. These findings reveal that there was a significant decrease in postoperative blood drainage in the DDAVP group ($p<0.05$). Overall blood product utilization was significantly less in the DDAVP group (1 unit/patient, compared with 2.2±1.4 units/patient) ($p<0.001$). There was also a reduction in utilization of fresh frozen plasma which was nonsignificant and a significant reduction in red cell usage in the DDAVP group ($p<0.05$). Only one patient in the DDAVP group required reoperation who had a surgical bleeding.

**Changes in hematologic variables after DDAVP (Fig 1 and 2, Table IV).** To elucidate the mechanism by which DDAVP achieves a reduction in bleeding and blood product utilization, hematologic variables were measured immediately before DDAVP administration and at 1, 4 and 24 hours afterwards.

Although the bleeding time increased in early postoperative period, it subsided to normal ranges in the first postoperative day (Fig 1 B). The mean platelet count remained unchanged after DDAVP (Fig 2).

**Table II:** Baseline comparison of preoperative, operative and early postoperative variables in the desmopressin and control groups.

| Variable | Desmopressin (n=15) | Control (n=15) | p value |
|---|---|---|---|
| Preoperative | | | |
| Age (mean)(year) | 41 ±9 | 41 ±7 | NS |
| Prior cardiac surgery | 2 (13%) | 3(20%) | NS |
| Hematocrit (%) | 37 ±6 | 38 ±4 | NS |
| Platelet count ($10^3$/mm$^3$) | 237 ±58 | 210 ±42 | NS |
| Bleeding time (min) | 1 ±0.07 | 1.3 ±0.9 | NS |
| Prothrombin time (sec) | 14.1 ±1.2 | 13.5 ±1 | NS |
| Operative | | | |
| Duration of operation (min) | 172 ±32 | 184 ±65 | NS |
| Duration of extracorporeal circulation (min) | 98 ±30 | 97 ±29 | NS |
| Early postoperative | | | |
| Hematocrit (%) | 28 ±5 | 29 ±2 | NS |
| Platelet count ($10^3$/mm$^3$) | 128 ±61 | 121 ±32 | NS |
| Bleeding time (min) | 1.3 ±0.6 | 1.8 ±0.8 | NS |
| Prothrombin time (sec) | 17.9 ±2.6 | 17.1 ±2 | NS |

After administration of DDAVP the increase in FVIII procoagulant activity reached maximal ranges at the 24 th postoperative hour (Fig 2). The prothrombin time demonstrated shortening within 1 hour after DDAVP administration and at later intervals as well. Fibrinogen levels rose significantly at 4 and 24 hours after DDAVP infusion. Serum potassium remained unchanged before and after administration of DDAVP.

Fibrinogen, FVIII procoagulant activity (FVIII: C), platelet count bleeding time, prothrombin time in DDAVP and control group are showen Table V.

Serum sodium, creatinine, and urea levels increased slightly after DDAVP, but the difference was not significant. Although after administration of DDAVP there was a decrease in the levels, as a clinical protocol we prefer to hold these levels under 25%.

**Table III:** Postoperative bleeding, blood product utilization and reoperation rates in DDAVP and control groups after treatment.

| Variable | Desmopressin (n=15) | Control (n=15) | p value |
|---|---|---|---|
| Mediastinal tube drainage (ml/h) | 11.7±7 | 24.5±20.8 | p<0.05 |
| Blood product utilization (units/patient) | | | |
| Platelets | — | — | |
| Fresh frozen plasma | 1.8±1 | 1.8±0.7 | NS |
| Red blood cells | 1 | 2.2±1.4 | p<0.05 |
| Total | 2.8±1 | 4.1±2 | p<0.05 |
| Hematocrit after 24 hours (%) | 25.0±3 | 28.0±3 | p<0.05 |
| Reoperation for hemorrhage | 1 (6.6%) | — | |
| Generalized bleeding | — | — | |
| Localized bleeding | 1 | — | |
| Bleeding stopped | — | — | |

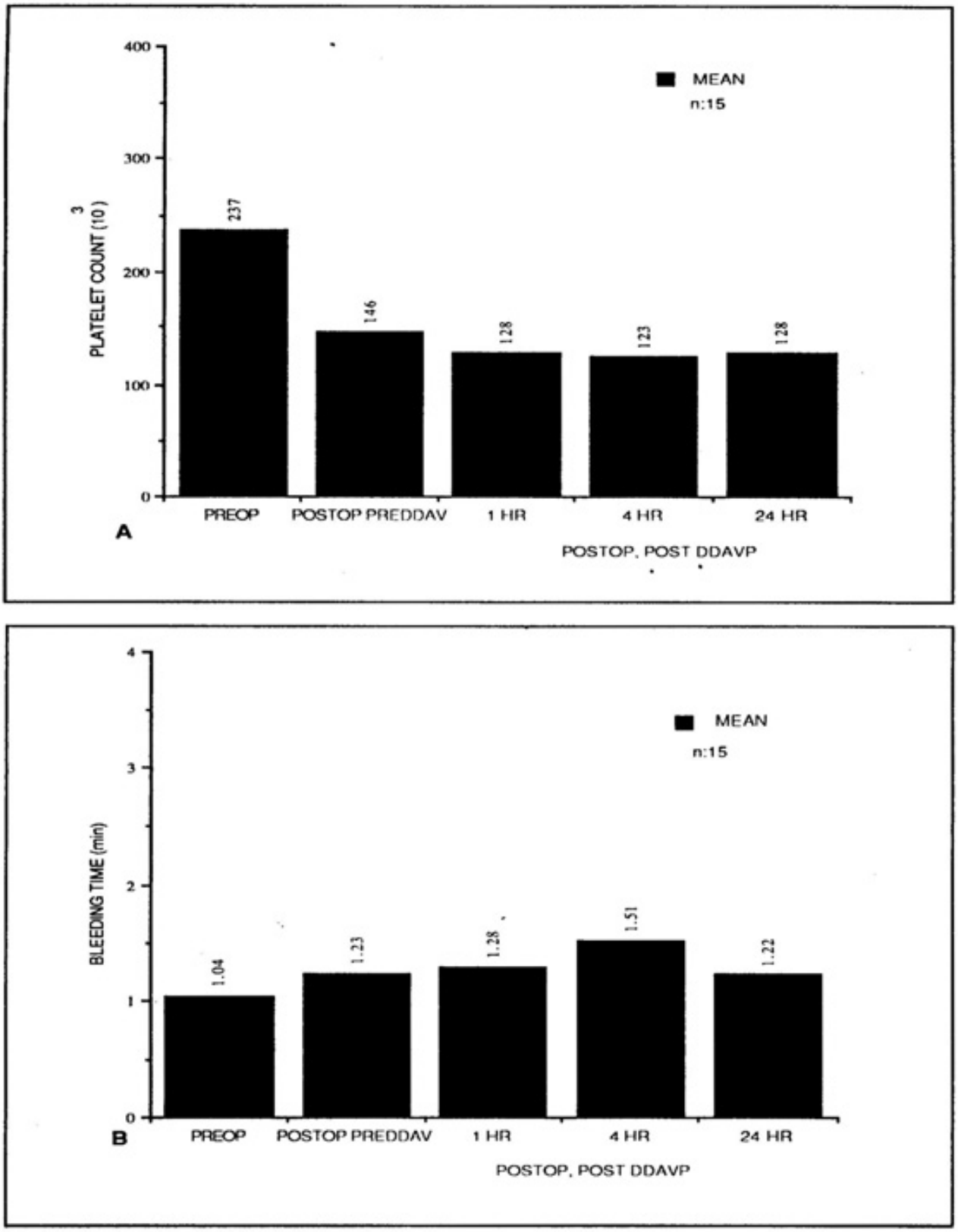


**Figure1: A** Platelet count and **B** template bleeding time, determined preoperatively (PREOP), early postoperatively (POSTOP PRE DDAVP), and at 1, 4 and 24 hours after desmopressin administration (POSTOP, POSTOP DDAVP).

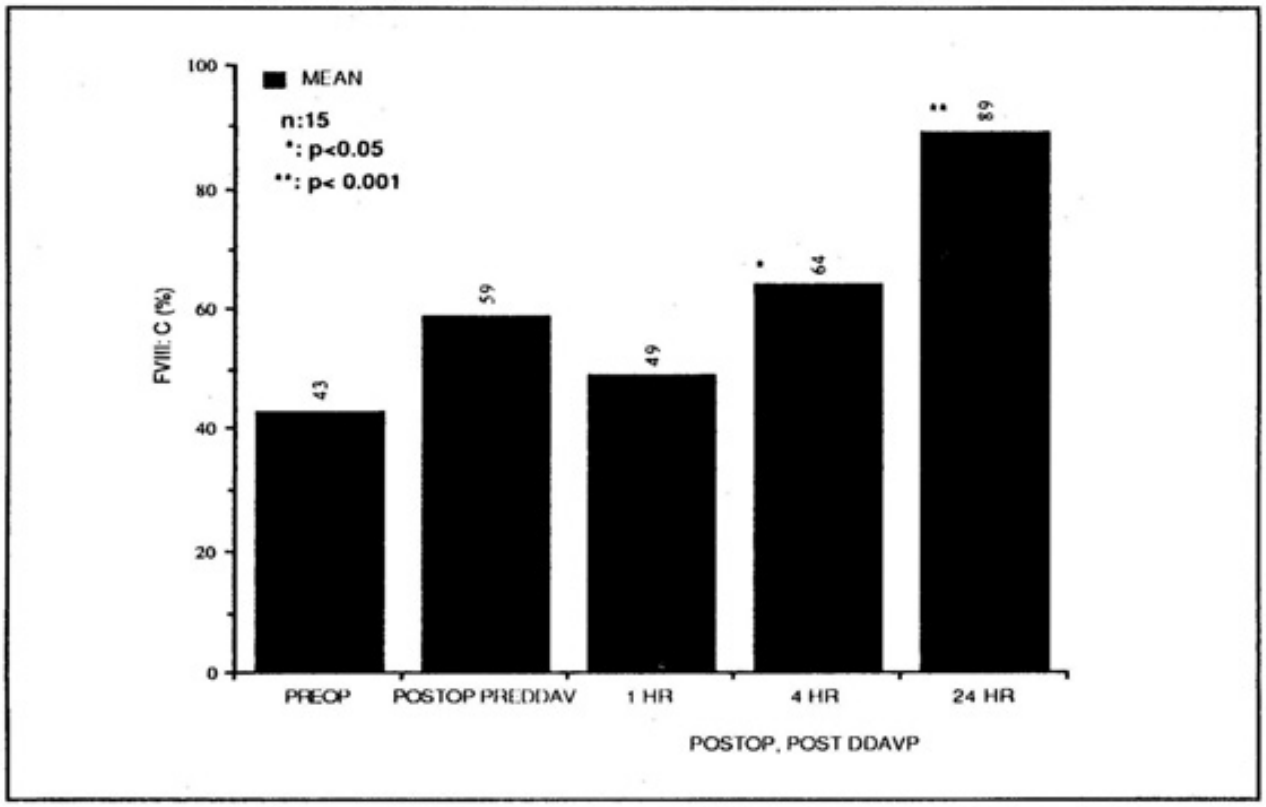


**Figure 2:** Factor VIII activities, determined preoperatively, early postoperatively (POSTOP PRE DDAVP), and at 1, 4, and 24 hours after desmopressin administiation (POSTOP, POST DDAVP)

## Discussion

The risk of transmission of blood born disease and the shortage of homologuous blood have led to a search for hemostatically effective agents (e.g. DDAVP and aprotinin).

During the first 24 hours of cardiac surgery, a tendency to bleed is commonly observed. This often requires transfusion of blood products. Many factors have been implicated in postoperative bleeding; including surgical causes of bleeding, dilutional coagulopathy, thrombocytopenia, qualitative platelet defects, inadequate reversal of heparin anticoagulation, and excessive administration of protamin [2-9]. DDAVP is an effective adjuvant in the

**Table IV:** Selected laboratory measurement before and after desmopressin administration

| | | Postoperative | | | |
|---|---|---|---|---|---|
| | | Before | After Desmopressin | | |
| | Preoperative | Desmopressin | 1 Hour | 4 Hours | 24 Hours |
| Prothrombin time (s) | 14.1±1.2 | 19.5±6.6 | 17.9±2.6 | 17±1.9 | 15.1±2.4* |
| Fibrinogen (mg/dl) | 290.0±112 | 259.0±75 | 277.0±104 | 409±207** | 479.0±122** |
| Fibrinogen-fibrin degradation products (µg/ml) | <5 | 5<20 | 5<20 | 5<20 | <5 |
| Hematocrit (%) | 37.0±6 | 40.0±4 | 28.0±5 | 27±5 | 25.0±3 |
| Serum sodium (mEq/L) | 141.0±3 | 140.0±4 | 144.0±4* | 147±6** | 145.0±4* |
| Serum potassium (mEq/L) | 4.3±0.3 | 4.0±0.4 | 3.9±0.6 | 4±0.3 | 4.0±0.4 |
| Serum creatine (mg/dl) | 0.8±0.1 | 0.8±0.1 | 0.8±0.1 | 1±0.1 | 0.8±0.2 |
| Serum urea (mg) | 28.4±7 | 30.2±7 | 31.1±6 | 31±7 | 32.8±7 |

* p<0.05, ** p<0.001 compared with postoperative value before desmopressin

**Table V:** Selected laboratory measurement in desmopressin and control group.

| | | Postoperative | | | |
|---|---|---|---|---|---|
| | | Before | After Desmopressin | | |
| | Preoperative | Desmopressin | 1 Hour | 4 Hours | 24 Hours |
| **Fibrinogen (mg/dl)** | | | | | |
| Desmopressin group | 290±112 | 259± 75 | 277±104 | 409±207 | 479±122 |
| Control group | 355±155 | 308±149 | 250±112 | 324±123 | 329±134 |
| p value | NS | NS | NS | NS | p< 0.001 |
| **FVIII:C (%)** | | | | | |
| Desmopressin group | 43±23 | 59±37 | 49±22 | 64±20 | 89±28 |
| Control group | 43±26 | 56±36 | 40±14 | 45±21 | 43±23 |
| p value | NS | NS | NS | p<0.05 | P<0.001 |
| **Platelet count ($10^3$)** | | | | | |
| Desmopressin group | 237±58 | 146±39 | 128±61 | 123±55 | 128±64 |
| Control group | 210±42 | 137±34 | 121±32 | 121±40 | 113±37 |
| p value | NS | NS | NS | NS | NS |
| **Bleeding time (min)** | | | | | |
| Desmopressin group | 1.1±0.07 | 1.2±0.1 | 1.3±0.6 | 1.5±0.8 | 1.2±0.6 |
| Control group | 1.3±0.9 | 1.2±0.3 | 1.7±0.8 | 1.8±0.9 | 1.3±0.5 |
| p value | NS | NS | NS | NS | NS |
| **Prothrombin time (s)** | | | | | |
| Desmopressin group | 14.1±1.2 | 19.5±6.6 | 17.9±2.6 | 17.2±1.9 | 15.1±2.4 |
| Control group | 13.5±1 | 16.6±1.4 | 17.1±2 | 16.1±1 | 14.3±0.8 |
| p value | NS | NS | NS | NS | NS |

management of blood drainage for severe platelet dysfunction and bleeding after cardiopulmonary bypass. DDAVP reduced total blood product utilization (From 2.2±1.4 to 1 unit/patient, p< 0.05). The most marked reduction was observed in platelet usage. At the same time, mediastinal bleeding was reduced as effectively in the DDAVP group as in the control group (Table III, IV). There was no significant change in bleeding time after DDAVP infusion. Fibrinogen levels and FVIII pro coagulant activity increased significantly (p<0.001, p<0.001).

Various studies have demonstrated that DDAVP achieved a shortening of bleeding time by increasing plasma levels of von Willebrand factor, with a resultant improvement in platelet adhesion. Desmoprensin may prefertially augment the release of the large multimers of von Willebrand factor, which are effective in mediating platelet adhesion [10-13].

There is also the possibility of producing a hypercoagulable state causing thrombotic complications, such as in coronary artery bypass vein grafts and deep vein thrombosis. However, this has not been demonstrated by any of the studies reported in the literature [11,14-18]. Even though this is a therotical concept, considering this thought, we made this study only in isolated valve procedures.

Salzman[16] have shown in a double blind trial that intra-operative use of DDAVP, significantly reduced blood loss in patients undergoing complex cardiac operations, excluding coronary artery bypass grafting.

Czer demonstrated, in a controlled trial that transfusion requirements, mediastinal bleeding more than 2 hours after termination of cardiopulmonary bypass were significantly reduced by the administration of DDAVP[17].

A double blind study by Roche on a group of patients having routine valve surgery and atrial septal defect repair did not demonstrate any dimmunition of total blood loss[18]. They specifically excluded patients needing emergency surgery, with known hemostatic defect, abnormal renal function and coronary bypass grafting[18]. In this study there was no reduction of blood loss in the group of patients at low risk for postoperative bleeding. This contrasts with the

results of Salzman et al., who used DDAVP prophylactically in a selected high risk group, and Czer et al who used it therapeutically in a group of patients already bleeding excessively [16,17].

In conclusion, administration of DDAVP reduced transfusion requirements, and blood loss in patients with severe platelet dysfunction and bleeding after cardiopulmonary bypass.

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