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The Role of Desmopressin Acetate in Patients Undergoing Coronary Artery Bypass Surgery

A Controlled Clinical Trial with Thromboelastographic Risk Stratification

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The role of desmopressin acetate in attenuating blood loss and reducing homologous blood component therapy after cardiopulmonary bypass is unclear. The purpose of this investigation was to identify a subgroup of patients that may benefit from desmopressin acetate therapy. One hundred fifteen patients completed a prospective randomized double-blind, placebo-controlled trial designed to evaluate the effect of desmopressin acetate (0.3 $\mu g \cdot kg^{-1}$) on mediastinal chest tube drainage after elective coronary artery bypass grafting surgery in patients with normal and abnormal platelet–fibrinogen function as diagnosed by the maximal amplitude (MA) on thromboelastographic (TEG) evaluation. The 115 patients evaluated were divided into two groups based on the MA of the post–cardiopulmonary bypass TEG tracing. Group 1 (TEG:MA > 50 mm) consisted of 86 patients, of whom 44 received desmopressin and 42 received placebo. Twenty-nine patients had abnormal platelet function (TEG:MA < 50 mm) and were designated as group 2. In group 2, 13 received desmopressin and 16 placebo. During the first 24 h after cardiopulmonary bypass, the placebo-treated patients in group 2 had significantly greater mediastinal chest tube drainage when compared to placebo patients in group 1 (1,352.6 ± 773.1 ml *vs.* 865.3 ± 384.4 ml, $P = 0.002$). In addition to increases in blood loss, group 2 placebo patients also were administered an increased number of blood products ($P < 0.05$). The desmopressin-treated patients in group 2 neither experienced increased mediastinal chest tube drainage nor received increased amounts of homologous blood products when compared to those in group 1. There was a difference in mediastinal chest tube drainage between placebo and desmopressin patients in group 2 (1,352.6 ± 773.1 *vs.* 881.2 ± 594.6, $P = 0.036$). There were no differences in the postoperative complications that were evaluated. The results suggest that the TEG (TEG:MA < 50 mm) can identify a patient population at risk for increased mediastinal chest tube drainage. Desmopressin administered to those patients was effective in decreasing the volume of mediastinal chest tube drainage. (Key words: Blood, coagulation: desmopressin. Measurement techniques: thromboelastography. Surgery, cardiac: coronary artery bypass grafting.)

NEARLY 250,000 coronary artery bypass graft operations in addition to other open heart procedures (valve replacement, aneurysmectomy, electrophysiologic surgery, and congenital abnormality repair) are performed each year. Associated with these procedures is a 3–7% incidence of postoperative hemorrhagic complications leading to mediastinal reexploration.[1,2] The pathophysiology of these hemorrhagic complications are multifactorial, and the risks associated with reoperation and blood transfusion are considerable.[3–6]

Uncommon causes of excessive mediastinal blood loss include a critical reduction in coagulation factors, residual anticoagulation, fibrinolysis, or excessive protamine administration.[7,8] The preponderance of evidence indicates, however, that the majority of nonsurgical bleeding is secondary to a variety of alterations in platelet physiology, function, and number.[9–11] The contact of blood with synthetic surfaces during extracorporeal circulation produces platelet activation with subsequent adhesion, activation, and degranulation. In addition, dilution by an asanguineous priming solution, the mechanical damage produced by multiple blood/gas interfaces, and the shear forces of mechanical perfusion further reduce platelet number and function.[12,13]

Because nonsurgical bleeding is a major concern after cardiopulmonary bypass (CPB), numerous investigations have focused on decreasing postoperative platelet dysfunction.[14,15] One therapeutic intervention that may affect the clinical measures of post-CPB nonsurgical bleeding is desmopressin acetate (DDAVP). Despite a number of evaluations (table 1), many of which have found no benefit from DDAVP, this therapy may be useful in a specific subset of patients. The differences in operative procedures, bypass time, and study design make the previous studies difficult to interpret and thus make it even more difficult to determine which patient may have benefited from DDAVP administration. The purpose of this investigation was to identify a group of patients that may benefit from DDAVP therapy.

Previous studies evaluating the efficacy of DDAVP did not identify patients at high-risk for post-CPB bleeding and focus on that subgroup. The work of Spiess *et al.*[25] and Tuman *et al.*[26] suggests that the thromboelastograph (TEG) may be able to identify accurately a subset of patients that develop severe post-CPB platelet–fibrinogen dysfunction and are at risk for excessive bleeding. This group of patients at increased risk for excessive mediastinal chest tube drainage (MCTD) (approximately 20%[17] of CPB procedures) has not been identified in the previous evaluations of DDAVP. The inclusion of the much larger

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TABLE 1. Comparison of Major Clinical Evaluations of Desmopressin in Reducing Post–Cardiopulmonary Bypass Blood Loss and Transfusion Requirements

Authors	Study Design	n	Population	Cardiopulmonary Bypass Time (min)		Blood Loss (ml)		Transfusions
				DDAVP	Placebo	DDAVP	Placebo	
Salzman *et al.*[16]	Randomized double-blind placebo-controlled	70	High-risk	144	159	1317	2210	Decreased
Czer *et al.*[2]	Case-controlled	39	1^0 + high-risk	156	155	1642	1574	Decreased
Rocha *et al.*[17]	Randomized double-blind placebo-controlled	100	High-risk	93	94	778	911	No change
Hackmann *et al.*[18]	Randomized double-blind placebo-controlled	150	1^0 + high-risk	168	161	865	738	No change
Brown *et al.*[19]	Randomized double-blind placebo-controlled	20	1^0	109	89	879	803	No change
Hedderich *et al.*[20]	Randomized double-blind placebo-controlled	62	1^0 + repeat	89	92	871	1051	No change
Anderson *et al.*[21]	Randomized double-blind placebo-controlled	19	1^0	70	69	852	1020	No change
Frankville *et al.*[22]	Randomized double-blind placebo-controlled	60	1^0	51	51	687	790	No change
Lazenby *et al.*[23]	Randomized double-blind placebo-controlled	60	1^0	83	86	701	771	No change
LoCicero *et al.*[24]	Retrospective with age and sex-matched controls	165	1^0	124	124	1306	896	Increased

High-risk procedures for post–cardiopulmonary bypass blood loss are considered valve replacement, repeat operation, and aneurysmectomy resection. Primary cardiopulmonary bypass surgery (1^0) is considered less a risk factor for post–cardiopulmonary bypass blood loss. Values are expressed as means of respective studies.
DDAVP = desmopressin acetate.

group of low-risk patients may have obscured any significant effects from the DDAVP administration in the patients at increased risk for excessive MCTD. This study is a prospective, randomized, double-blind, placebo-controlled evaluation of the efficacy of DDAVP in decreasing post-CPB blood loss and transfusion therapy in patients predicted by TEG measurements to be at low and high risk for excessive mediastinal blood loss.

Materials and Methods

After protocol approval by the Clinical Investigation committee, written informed consent was obtained from 118 patients, and 115 patients completed a randomized, placebo-controlled double-blind evaluation of the effect of DDAVP on post-CPB bleeding. Exclusion criteria included preoperative anticoagulation or aspirin therapy within 1 week of surgery, postoperative evidence of fibrinolysis ($A_{60}/MA < 0.85$, where MA = maximal amplitude and A_{60} = amplitude 60 min after MA), or reexploration secondary to surgical bleeding. A computer-generated random-number table was used to assign patients to receive either DDAVP (0.3 $\mu g \cdot kg^{-1}$, Rorer Pharmaceutical, Fort Washington, PA) diluted in 50 ml normal saline or 50 ml normal saline alone.

Anesthetic and Surgical Techniques

All antianginal medications were administered on the day of surgery in addition to intramuscular morphine (0.1 $mg \cdot kg^{-1}$) in combination with scopolamine (0.4 mg) or 1 mg oral lorazepam. After the insertion of intravenous, pulmonary, and arterial catheters, anesthesia was induced and maintained with fentanyl (40–60 $\mu g \cdot kg^{-1}$, total dose) in combination with midazolam (10 mg) and isoflurane (0–1%). Neuromuscular blockade was achieved and maintained with either pancuronium or vecuronium.

A Sarns roller pump with a 40-μm arterial filter and membrane oxygenator (Bentley Univax, Baxter Healthcare, Irvine, CA) were used for the CPB apparatus. Pump prime consisted of 2.2 l lactated Ringers solution, 50 mEq sodium bicarbonate, 10,000 U beef lung heparin (Upjohn, Kalamazoo, MI), and 1 g cephapirin. After anticoagulation with heparin (300 $U \cdot kg^{-1}$ beef lung heparin), injected into the right atrium, the aortic and venous cannulas were inserted. Systemic anticoagulation was verified by an activated clotting time (ACT) (Hemachron 400, International Technidyne, Edison, NJ) > 400 s, and moderate hypothermic (28–30° C) CPB was initiated. The cardiac index was maintained at 2.4 $l \cdot min^{-1} \cdot m^{2-1}$ during normothermia and at 1.8 $l \cdot min^{-1} \cdot m^{2-1}$ during hypothermia. During CPB, α-stat methodology was used for pH management, and the ACT was maintained > 480 s.

After ventricular fibrillation and placement of the aortic cross clamp, myocardial protection was induced with cold hyperkalemic (K^+ = 20 mEq · l) 4:1 blood:crystalloid cardioplegia (15 $ml \cdot kg^{-1}$) and maintained with 4:1 blood: crystalloid cardioplegia (K^+ = 10 $mEq \cdot l^{-1}$) (7.5 $ml \cdot kg^{-1}$) every 20 min. In addition, topical cooling with iced saline was used to augment myocardial protection. After completion of the distal saphenous vein and internal mammary

artery grafts, the aortic cross clamp was removed. If ventricular fibrillation occurred during reperfusion, defibrillation (20 J) was performed. Epicardial pacing leads were placed, and when the bladder temperature was > 35° C the patients were separated from CPB. The protamine sulfate (Du Pont) dose was calculated using an automated protamine titration method (Hepcon 10, Hemotec Inc., Englewood, CA). The study medication was administered over 15 min, after protamine administration and return of the ACT to normal. After obtaining hemostasis, the mediastinal and thoracostomy tubes were positioned; the chest was closed; and the patient was transported to the intensive care unit.

In the immediate post-CPB period, the remaining volume in the CPB machine was drained, washed with normal saline, concentrated, and made available for reinfusion. MCTD, autotransfusion volume, and transfusion requirements were recorded hourly for 24 h.

Packed red blood cells (PRBC) were administered for a hematocrit (HCT) < 24%. Pooled platelets, fresh frozen plasma, and cryoprecipitate were administered at the discretion of the attending surgeon and anesthesiologist based on quality of hemostasis, results of available hematologic studies, and amount of MCTD. The surgeon and anesthesiologist were blinded to the TEG parameters.

Postoperatively, all charts were reviewed for evidence of myocardial infarction as determined by new Q waves on a 12-lead electrocardiogram obtained on postoperative day 1 or peak myocardial creatinine kinase levels > 50 $IU \cdot l^{-1}$ (Kodak Ektachem, CK-MB, Eastman Kodak, Rochester, NY). Creatinine kinase levels were drawn upon admission to the intensive care unit and every 8 h for the next 24 h. In the event of mediastinal reexploration within 24 h, the reason for return to the operating room and operative diagnosis were recorded.

Hematologic Measurements

Preoperative blood samples were obtained by venipuncture the day before surgery for measurement of HCT, platelet count (Coulter C.A.S.H., Hialeah, FL), prothrombin time (PT), partial thromboplastin time (PTT) (Coag-A-Mate X2, General Diagnostics, Morris Plains, NJ), thrombin time, and fibrinogen (Fibrosystem BBL, Bectin Dickenson, Cockeysville, MD). A bleeding time was also performed (Simplate 2, Organon Teknika, Durham, NC). Subsequent blood samples were obtained from the arterial catheter and extension tubing (96 cm) after withdrawing 20 ml blood. The baseline TEG (Hellige Thromboelastograph, Haemoscope Corporation, Glenview, IL) was performed prior to anticoagulation. TEG determinations were performed using disposable plastic cuvettes and pistons. A small amount (0.35 ml) of whole uncitrated blood was instilled into the cuvette; the pin was lowered; and a thin layer of liquid paraffin was placed on top of the blood sample. The TEG tracing was measured for reaction time (23.6 ± 4.8 mm), clot build-up and cross-linking (α 36.0 ± 7.4°), platelet–fibrinogen interaction (TEG:MA 54.0 ± 5.6 mm) and fibrinolysis (A_{60}/MA ratio, > 0.85). A post-CPB TEG tracing was obtained after return to normal of the ACT in addition to determination of HCT, platelet count, PT, PTT, and fibrinogen. A final TEG tracing was obtained 45 min after the infusion of the study medication or just prior to leaving the operating room. The final set of hematologic measurements were obtained upon arrival in the intensive care unit (HCT, platelet count, PT, PTT, thrombin time, and fibrinogen). Patients were divided into two groups based upon TEG analysis. Group 1 consisted of patients with normal TEG parameters prior to and after separation from CPB. Group 2 consisted of patients with normal TEG parameters prior to CPB who demonstrated abnormal TEG values (TEG:MA < 50 mm) after CPB but prior to DDAVP or placebo administration (fig. 1).

Statistical Analysis

Descriptive statistics were generated and are expressed as mean ± standard deviation. Continuous variables were analyzed with analysis of variance (ANOVA) with covariance analysis to detect for significant interactive effects of other metric variables. The Kruskal-Wallis (KW) test was used to analyze for differences in ordinal variables (blood product administration), and the Fisher's Exact (FE) test was used for analysis of contingency tables. A forward stepwise linear regression model was applied to the group variables for the development of a predictive model for MCTD and transfusion therapy. Factors were assigned to the model in the order of decreasing value of the variables' F statistic. Variables were included in the

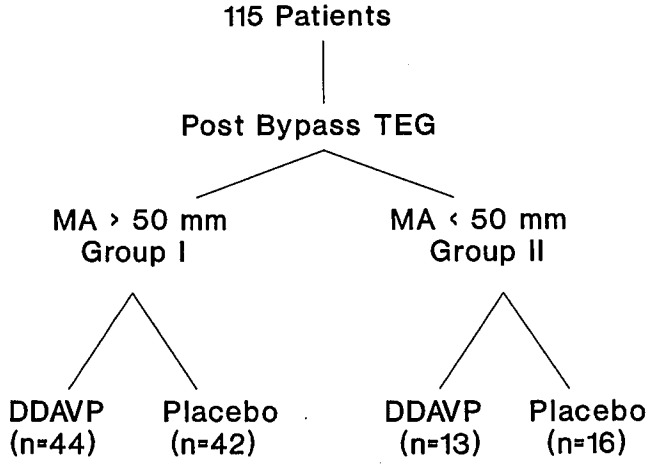

FIG. 1. The patient grouping for this study. The post–cardiopulmonary bypass thromboelastogram (TEG) was used to divide the patients into groups 1 and 2. Patients then were divided into placebo or desmopressin subgroups for analyses of post–cardiopulmonary bypass mediastinal chest tube drainage, transfusion therapy, and complications. MA = maximal amplitude; DDAVP = desmopressin acetate.

model if the F statistic was greater than 4 and if the variable strengthened the model. A P value < 0.05 was considered significant after correction for multiple comparisons.

Results

Demographic, surgical, and preoperative antianginal therapy are described in table 2. Figure 1 provides a diagram of patient grouping and numbers. The four attending surgeons were equally distributed between groups ($P = 0.74$, FE). The differences found between group 1 (TEG:MA > 50 post-CPB) and group 2 (TEG:MA < 50 post-CPB) were that group 2 patients were smaller (weight and body surface area [BSA]; $P < 0.05$, ANOVA) and had a greater proportion of women ($P = 0.023$, FE). Table 3 documents the hematologic and TEG parameters at the three prescribed test periods. No statistically significant differences were found in the pre-CPB measurements. After protamine titration, group 2 patients had significantly lower fibrinogen levels as well as α and MA:TEG parameters ($P < 0.05$, ANOVA). Forty-five minutes after infusion of the study medication, there was no difference in the fibrinogen levels ($P = 0.14$, ANOVA). Improvement in the fibrinogen level was accounted for by blood component administration (cryoprecipitate, fresh frozen plasma; $P < 0.05$, covariance analysis). However, α and MA were still significantly less in group 2. Covariance analysis indicated that the fibrinogen level and patient size were significant factors ($P < 0.05$) associated with the decrease in both α and MA. However, stepwise linear regression modeling indicated an only moderate predictive power ($r^2 = 0.28$) for those variables in predicting changes in the TEG:MA. Because the TEG:MA is primarily an indicator of platelet–fibrinogen interaction, the remainder of the regression model may be accounted for by platelet dysfunction inherent to CPB times of this duration. However, the presence of other undefined factors that influence the TEG:MA cannot be ruled out. In subgroup analysis, the group 2 placebo patients exhibited a shorter reaction time on the final TEG, and that group had less normalization ($P < 0.05$ ANOVA) of the TEG:MA when compared to the DDAVP-treated patients of group 2.

The results of postoperative MCTD are shown in table 4. The MCTD in the placebo-treated patients in group 2 was greater ($P = 0.0022$, ANOVA) when compared to group 1. The major differences were observed in the first 2 h in the intensive care unit. The increased volume of MCTD in the placebo patients of group 2 was attributed to the decrease in the platelet–fibrinogen interaction diagnosed by the TEG. The MCTD was also decreased in the DDAVP-treated patients in group 2 ($P = 0.036$, ANOVA) in comparison to placebo patients in group 2. Because of the lack of significant interactive effects ($P > 0.05$ covariance analysis) from other variables, the differences were attributed to the DDAVP administration. Analysis between subgroups of group 1 revealed no differences in MCTD. However, the null hypothesis still cannot be accepted because the calculated power based on the standardized differences between group 1 subgroups at 24 h is only 35%. To attain a power of 80%, 350 patients with normal TEG parameters post-CPB would need to be studied to conclude that no statistically significant decrease in MCTD was gained from the administration of DDAVP.

The number of patients that experienced excessive MCTD (> 300 ml × 1 h, > 150 ml × 2 consecutive h, or > 1,200 ml for 24 h) are presented in table 5. The accuracy (true nonbleeders + true bleeders/total) of the TEG:MA in predicting postoperative blood loss in the placebo patients was 78% (37 + 8/58). The false negative rate was 12% (5/42) and the false positive rate 50% (8/16). It is possible that the false positive rate was influenced

TABLE 2. Comparison of Demographic, Medication, and Surgical Characteristics

Variable	Group 1		Group 2	
	Desmopressin	Placebo	Desmopressin	Placebo
n	44	42	13	16
age (yr)	61.5 ± 9.3	60.9 ± 9.7	58.8 ± 10.7	65.8 ± 10.0
Height (cm)	174.7 ± 9.4	173.2 ± 9.6	168.4 ± 6.9	170.7 ± 12.6
Weight (kg)	83.6 ± 10.2	85.1 ± 16.0	71.3 ± 10.6*	75.8 ± 14.7*
Body surface area (m^2)	1.99 ± 0.16	1.98 ± 0.21	1.81 ± 0.16*	1.86 ± 0.24*
Men/women	40/4	36/6	9/4*	11/5*
Ejection fraction	53.6 ± 13.6	51.0 ± 13.8	53.0 ± 12.9	58.2 ± 11.4
Cardiopulmonary bypass time (min)	127.6 ± 35.9	131.7 ± 31.9	131.3 ± 41.2	136.1 ± 37.3
Number of vein grafts	3.2 ± 0.74	3.3 ± 0.89	3.2 ± 0.59	3.5 ± 0.52
Internal mammary artery	35	30	9	8
Repeat coronary artery bypass graft	6	7	1	1
Calcium-channel antagonists	31	24	9	12
Nitrates	27	30	9	11
β-Blockers	27	27	9	12

Values are expressed as mean ± standard deviation.

* $P < 0.05$, group 2 compared to group 1 (Fisher's exact test). No differences were dicserned between subgroups.

TABLE 3. Comparison of Hematologic and Thromboelastographic Parameters

Variable	Pre-Cardiopulmonary Bypass				Post-Cardiopulmonary Bypass				Intensive Care Unit			
	Group 1		Group 2		Group 1		Group 2		Group 1		Group 2	
	DDAVP	Placebo	DDAVP	Placebo	DDAVP	Placebo	DDAVP	Placebo	DDAVP	Placebo	DDAVP	Placebo
Hematocrit (%)	40.3 ± 5.1	41.2 ± 4.4	41.7 ± 6.1	38.6 ± 5.5	23.1 ± 2.6	23.5 ± 2.7	22.2 ± 4.2	21.5 ± 4.5	25.1 ± 3.6	24.2 ± 4.3	23.8 ± 3.9	23.8 ± 4.0
PLT (10^3/mm^3)	257.5 ± 74.1	260.3 ± 79.7	277.8 ± 44.3	292.5 ± 91.3	125.7 ± 51.9	116.5 ± 45.9	117.6 ± 25.4	101.0 ± 19.5	134.2 ± 47.9	136.3 ± 48.7	134.5 ± 32.3	126.5 ± 42.2
PT (s)	11.7 ± 0.8	11.6 ± 0.6	11.9 ± 0.8	11.4 ± 1.0	16.4 ± 2.2	16.7 ± 1.4	17.3 ± 1.5	17.1 ± 1.0	15.9 ± 1.4	15.9 ± 1.6	16.8 ± 1.9	16.3 ± 1.4
PTT (s)	30.7 ± 4.9	30.2 ± 4.4	30.7 ± 4.2	30.6 ± 3.6	39.7 ± 10.6	39.0 ± 4.0	40.0 ± 4.7	43.6 ± 4.3	36.2 ± 4.2	38.9 ± 7.0	39.1 ± 6.1	42.3 ± 5.3
TT (s)	9.5 ± 1.1	9.4 ± 1.2	8.5 ± 0.9	9.0 ± 0.9					8.4 ± 1.3	8.7 ± 1.2	7.9 ± 1.2	8.5 ± 0.7
BT (s)	336.6 ± 87.7	303.4 ± 67.9	305.5 ± 69.0	286.9 ± 58.9								
FIB (mg/dl)	388.7 ± 98.7	380.4 ± 67.9	364.4 ± 66.8	372.9 ± 93.5	189.1 ± 48.7	175.2 ± 28.9	149.9 ± 25.1*	148.9 ± 48.6*	193.1 ± 51.3	181.5 ± 45.2	160.9 ± 38.2	167.1 ± 41.5
R (mm)	16.1 ± 4.3	16.0 ± 6.1	12.9 ± 2.3	14.9 ± 7.6	14.9 ± 5.7	16.0 ± 6.1	16.1 ± 4.1	14.7 ± 9.5	11.7 ± 2.7	12.4 ± 3.3	13.3 ± 3.6	9.5 ± 4.6*
α (·)	36.6 ± 10.8	36.9 ± 11.4	40.4 ± 10.0	36.8 ± 10.7	48.4 ± 8.9	46.9 ± 11.4	39.9 ± 9.3*	37.1 ± 7.8*	47.9 ± 8.8	49.3 ± 8.9	41.3 ± 9.3*	42.6 ± 8.9*
MA (mm)	57.6 ± 8.1	59.6 ± 7.3	59.9 ± 6.3	55.9 ± 7.6	58.4 ± 6.1	59.6 ± 7.3	42.9 ± 3.9*	41.7 ± 7.3*	56.5 ± 6.3	55.6 ± 6.6	47.9 ± 8.8*	44.7 ± 6.7*
A60 (mm)	52.4 ± 9.6	54.9 ± 8.2	55.1 ± 9.2	51.6 ± 7.1	53.1 ± 6.4	55.2 ± 8.3	39.6 ± 4.8*	39.1 ± 6.5*	52.9 ± 7.4	51.4 ± 6.1	44.2 ± 7.1*	41.5 ± 5.9*

* $P < 0.05$ (ANOVA) comparing group 2 subgroups to group 1 subgroups.

by the increased amount of platelets and fresh frozen plasma received by the group 2 placebo patients immediately post-CPB.

The transfusion requirements are presented in table 6. There was no difference in either group in regard to the number of patients ($P = 0.056$, FE) or the number of PRBC units ($P = 0.083$, KW) transfused during CPB. The potential differences in BSA and hemodilution were attenuated by the variability in preoperative HCT and duration of CPB ($P < 0.05$, covariance analysis). Immediately post-CPB, more group 2 placebo patients ($P < 0.05$, FE) received more blood products (platelets, fresh frozen plasma, cryoprecipitate; $P < 0.05$, each KW) when compared to the placebo-treated patients in group 1. There were no statistically significant differences between placebo- and DDAVP-treated patients in either group.

In the intensive care unit, significantly more placebo-treated patients in group 2 received fresh frozen plasma in the first 8 h ($P = 0.045$, FE). Combining the immediate post-CPB period and the first 4 h in the intensive care unit did result in significant differences in number of units of platelets transfused ($P = 0.046$, KW) between placebo and DDAVP-treated patients in group 2. Significant differences were also observed in group 1. In addition, significantly fewer DDAVP-treated patients in group 1 received fewer units of PRBCs, platelets, and fresh frozen plasma (table 6). DDAVP administration was the significant factor (covariance analysis) in producing those differences.

Analysis of the 24-h transfusion requirements by a forward stepwise linear regression model indicated that BSA ($\beta = -8.1$), CPB duration ($\beta = 0.1$), MCTD ($\beta = 0.016$), and the post-CPB TEG:MA ($\beta = -0.14$) were responsible for the majority ($r^2 = 69.8\%$, standard error = 5.6, constant = 7.7) of the variability between the regression model and the actual transfusion therapy. Other than differences in MCTD and transfusion requirements, there were no differences in measured outcomes between groups for cardiogenic failure (intraaortic balloon pump), non–Q-wave (creatinine kinase > 50 IU · l^{-1}) or Q-wave myocardial infarction, reexploration, or death (table 7). Three patients were excluded from the study, one for fibrinolysis ($A_{60}/MA = 0.65$) and two for surgical bleeding diagnosed during mediastinal exploration. Although adverse effects of DDAVP administration were not observed, limitations in the study size could have precluded the detection of low-frequency complications such as thrombotic events and severe hypotension.

Discussion

Cardiac surgical procedures using extracorporeal circulation are performed commonly in the United States. However, because substantial numbers of patients receive

TABLE 4. Comparison of Postoperative Mediastinal Chest Tube Drainage

Variable	Group 1		Group 2	
	Desmopressin	Placebo	Desmopressin	Placebo
1st hour	104.2 ± 109.6	115.1 ± 82.3	135.1 ± 90.1*	242.3 ± 142.2†
2nd hour	64.3 ± 47.2	90.2 ± 67.8	48.1 ± 38.8*	174.0 ± 183.5†
3rd hour	66.7 ± 62.8	71.2 ± 51.2	70.0 ± 73.7	97.1 ± 84.7
4th hour	51.8 ± 38.4	66.7 ± 68.1	61.9 ± 49.5	104.4 ± 91.6
4-h total	289.9 ± 164.5	344.6 ± 187.2	315.0 ± 161.6*	548.2 ± 392.4†
8-h total	413.2 ± 200.5	483.9 ± 229.8	471.2 ± 257.9*	833.7 ± 545.6†
24-h total	769.6 ± 251.5	865.3 ± 384.4	881.2 ± 594.6*	1352.6 ± 773.1†

Values are milliliters presented as mean ± standard deviation.

During the first 2 h in the intensive care unit, group 2 placebo-treated patients experienced more mediastinal chest tube drainage. The attenuation in blood loss in the DDAVP patients in group 2 was attributable to the administration of desmopressin (*$P < 0.05$, ANOVA) when compared with the group 2 placebo patients. This early difference was lost by the 3rd and 4th hour secondary to transfusion of fresh frozen plasma and platelets ($P < 0.05$, covariance analysis). However, the differences observed in the first 2 h persisted throughout the 24-h study period.

†$P < 0.005$ (ANOVA) when compared to placebo patients in group 1.

homologous blood products[27,28] and 3–7% may require reexploration secondary to excessive bleeding, there has been great interest in therapies and methods to improve postoperative hemostasis and reduce the need for blood product administration.[29,30] The hemostatic defects associated with CPB are complex, and the reasons for excessive MCTD are multifactorial. However, qualitative and quantitative platelet defects have been shown to be an important factor[9–11,29,30] especially with prolonged CPB times.[10] These defects arise from platelet interaction with the synthetic surfaces of the CPB apparatus, platelet destruction, and sequestration.[31–33] Contact with synthetic surfaces results in α-granule release with subsequent reduced aggregation and adhesiveness of the platelets.[10] Although these defects are short-lived (1–2 h), they contribute to excessive blood loss and the increased use of homologous blood and blood component therapy.

DDAVP is one form of pharmacologic therapy that may be efficacious in decreasing the platelet dysfunction,[26] reducing early post-CPB blood loss[17] and total blood loss in high-risk patients with prolonged CPB times.[16] DDAVP enhances platelet effectiveness by increasing plasma levels of high multimetric von Willebrand factor,[34] factor $VIII_c$ (3–4×), $VIII_{ag}$ (2–3×)[34] and by other undefined mechanisms.[35] Despite known platelet-enhancing effects, the appropriate role for DDAVP in elective CABG procedures is unclear. Although criticized for excessive MCTD, the results of Salzman *et al.*[16] suggest that DDAVP may be effective in decreasing MCTD in high-risk patients. A subsequent study by Rocha *et al.*[17] did not confirm those results, however; there were major differences in the CPB duration and possibly the magnitude of platelet dysfunction. In a separate study, Czer *et al.*[2] concluded that DDAVP was an effective treatment in patients with excessive MCTD. However, their results are questioned because 9 of the 16 control patients had a localized bleeding site during reoperation. Other studies evaluating the role of DDAVP in reducing post-CPB bleeding were skewed by the inclusion of patients undergoing valve operations, small sample size, and the failure to identify a group of patients who were at higher risk for post-CPB platelet dysfunction (table 1). The current study was designed to address these criticisms. The inclusion criteria attempted to gather an adequate-size homogenous group of patients and identify a group of patients at higher risk for post-CPB bleeding diagnosed by whole-blood viscoelastic co-

TABLE 5. Comparison of Excessive Postoperative Mediastinal Chest Tube Drainage

Variable	Group 1		Group 2	
	Desmopressin	Placebo	Desmopressin	Placebo
n	44	42	13	16
>150 ml × 2 h	1	2	2	3
>300 ml × 1 h	2*	3*	1	5
>1200 ml × 24 h	2*	4*	3	8
Combined abnormal MCTD	3*	5*	3	8

MCTD = mediastinal chest tube drainage.

*$P < 0.05$ (Fisher's exact test) comparing group 1 desmopressin and placebo patients to group 2 placebo patients. There were no differences between desmopressin acetate– and placebo-treated patients in group 1.

TABLE 6. Comparison of Transfusion Requirements Between Groups

Variable	Group 1		Group 2	
	Desmopressin	Placebo	Desmopressin	Placebo
Cardiopulmonary bypass				
PRBC (units/patients)	54/16	43/18	22/7	30/11
Post-cardiopulmonary bypass				
PRBC (units/patients)	29/14	35/18	14/4	28/9
PLT (units/patients)	36/6	30/5*	24/4	60*/7
FFP (units/patients)	8/4	10/5*	8/3	18*/6
CRYO (units/patients)	0/0	0/0	0/0	20*/2
Intensive care unit 4-h total				
PRBC (units/patients)	23†/12†	42/22	15/7	15/8
PLT (units/patients)	0†/0†	48/8	12/2	12/2
FFP (units/patients)	2†/1	12/6	4/1	9/5
CRYO (units/patients)	0/0	10/1	0/0	10/1
Autotransfusion (ml)	293.0 ± 95.7	420.0 ± 218.6	316.4 ± 152.6	362.5 ± 85.4
CPB pump residual (ml)	481.6 ± 294.7	428.9 ± 213.7	400.1 ± 122.4	424.1 ± 234.5
Intensive care unit 8-h total				
PRBC (units/patients)	30†/13†	53/23	20/8	26/11
PLT (units/patients)	0†/0†	48/8	12/2	24/4
FFP (units/patients)	4†/2	14/7*	4/1	16/7‡
CRYO (units/patients)	0/0	20/2	0/0	20/2
Intensive care unit 24-h total				
PRBC (units/patients)	38†/16†	75/25	31/9	35/12
PLT (units/patients)	6†/1†	60/9	18/3	24/4
FFP (units/patients)	4†/2	16/7*	15/4	19/7
CRYO (units/patients)	0/0	20/2	0/0	20/2

A Fisher's exact test was used for analysis of numbers of patients transfused; a Kruskal-Wallis test was used for analysis of the differences in the number of units of blood products transfused.

PRBC = packed red blood cells; PLT = platelets; FFP = fresh frozen platelets; CRYO = cryoprecipitate; CPB = cardiopulmonary bypass.

* $P < 0.05$ for the comparison of group 1 and group 2 placebo-treated patients.

† $P < 0.05$ for the comparison of group 1 subgroups.

‡ $P < 0.05$ for the comparison of group 2 subgroups.

agulation parameters. The second criterion was based on evaluations that suggest that the TEG:MA can accurately (85%) assess risk for excessive postoperative MCTD.[25,26]

Our results demonstrate the application of TEG parameters to be useful in discriminating which patients are at risk for a larger volume of MCTD. Overall, the TEG provided appropriate risk stratification based on a qualitative platelet–fibrinogen abnormality in an easy, rapid, and reliable manner. This is confirmed by the increased MCTD experienced by the group 2 placebo patients (table 4), the lack of other measured variables influencing those results, and the inclusion of the TEG:MA as a significant factor in the regression model for postoperative blood loss. The accuracy, however, was slightly less (78%) when compared to the results of Spiess *et al.*[25] and Tuman *et al.*[26] (85%). This difference could be related to the attenuation in blood loss secondary to the increased volume of platelets and fresh frozen plasma that was administered to the group 2 placebo-treated patients.

In this evaluation of patients undergoing elective CABG, DDAVP was effective in reducing blood loss and blood component administration in the early post-CPB period in patients at risk for increased MCTD (TEG:MA < 50). Platelet aggregation is maximally reduced at 1–4

TABLE 7. Comparison of Postoperative Complications

	Group 1		Group 2	
	Desmopressin	Placebo	Desmopressin	Placebo
n	44	42	13	16
Intraaortic balloon pump	4	1	0	1
Non–Q-wave myocardial infarction	8	6	1	1
Q-wave myocardial infarction	1	0	0	0
Death	2	0	0	0
Mediastinal reexploration	0	0	0	2

No differences in the occurance of listed events between groups or subgroups (Fisher's exact test).

h post-CPB.[36] Group 2 patients that received DDAVP had significantly less MCTD than did placebo patients. This may be accounted for by the ability of DDAVP to enhance platelet aggregation during this critical time period. These results are consistent with the onset of action of intravenous DDAVP,† the decrease in early blood loss period observed by Rocha *et al.*,[17] and the time course of platelet dysfunction after CPB.[10] Despite equivalent normalization of fibrinogen and significant differences in early platelet and plasma administration, the recovery of the TEG:MA at 45 min post-CPB was greater in the DDAVP-treated group 2 patients. More importantly, MCTD was significantly reduced in this increased risk group. With appropriate risk stratification by a post-CPB TEG:MA < 50 mm, the results support the conclusion that DDAVP is effective in decreasing clinically important measures of blood loss and transfusion therapy.

DDAVP was also effective in decreasing transfusion therapy in patients with a normal TEG:MA post-CPB. One possible explanation may be reversal of platelet dysfunction not measured by the TEG. However, the results must be viewed with caution. The linear regression model showed good correlation between predicted and observed transfusion practices based on BSA, CPB duration, MCTD, and the TEG:MA post-CPB. Overall, PRBC administration was consistent with the 75% patient transfusion rate reported in a recent multicenter study.[27] Because PRBC transfusions were limited to patients with a HCT < 24% and there were no differences in the autotransfusion of MCTD or administration of residual CPB volume, we believe that the differences in the PRBC transfusions in group 1 are valid. Although there were no differences in the total volume to MCTD, it is possible that there were differences in the HCT of the shed blood. Although this variable was not measured in our study, a similar work by Bidstrup and associates[14] using aprotinin found that the hemoglobin loss was three times less in the aprotinin patients because the MCTD quickly became serous. However, clinical confirmation for that explanation is necessary. The linear regression model estimated that 70% of the variability in the transfusion practice could be significantly attributed to the MCTD, DDAVP administration TEG:MA post-CPB, the BSA, and bypass duration. The other 30% could not be accounted for by measured variables. However, the transfusion percentage for platelets and fresh frozen plasma were significantly higher[27] than reported values. This may represent some aspect of inappropriate transfusion therapy and thus account for the remainder of the variability. Previous criteria for excessive MCTD ranges from 10 ml · kg^{-1} · h^{-1}[37] to 250 ml during the first 2 h and 100–150 ml/h thereafter.[37,38] Using a liberal definition of excessive MCTD (250 ml × 2 h), one half of the placebo patients in group 1 who received platelets (four of eight) and fresh frozen plasma (three of six) did not meet the definition of excessive MCTD and patients in the DDAVP group did not receive platelets or fresh frozen plasma despite meeting criteria for MCTD. Overall, a number of patients received platelets and fresh frozen plasma transfusions with no apparent indication for such therapy. Thus, the transfusion results in group 1 should be viewed with caution until confirmatory data in studies that standardize transfusion practices for platelets and fresh frozen plasma are obtained.

In conclusion, the data support the use of the TEG for risk stratification of patients when evaluating post-CPB coagulation status. The use of DDAVP in patients with a TEG:MA < 50 mm post-CPB significantly reduces MCTD and is clearly indicated. Additional controlled studies are necessary to determine the role of DDAVP in patients with a normal TEG:MA and moderate to prolonged CPB times.

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