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A Study of Desmopressin and Blood Loss during Spinal Fusion for Neuromuscular Scoliosis

A Randomized, Controlled, Double-Blinded Study

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***Background*: Studies examining the use of desmopressin acetate (DDAVP) have shown variable results in DDAVP's efficacy for reducing blood loss. Studies of adults having cardiac surgery and of children having spinal fusion have suggested that patients with complicated medical histories and complex surgical procedures may benefit from use of DDAVP. Therefore, this study was designed to examine the homeostatic effects of DDAVP in children with severe cerebral palsy undergoing spinal fusion.**

***Methods*: A randomized, double-blinded, and placebo-controlled trial of DDAVP was designed to enroll 40 patients. However, termination of the study was advised by the Institutional Review Board after 21 patients were enrolled. All patients had spastic quadriplegic-type cerebral palsy and were randomly assigned to one of two groups. The DDAVP group received 0.3 μg/kg DDAVP in 100 ml normal saline, and the placebo group received normal saline alone. All patients were anesthetized with nitrous oxide, oxygen, isoflurane, and fentanyl. Factor VIIIC and von Willebrand's factor (vWF) concentrations were measured in blood drawn before DDAVP infusion and 1 h after infusion. Blood pressure was maintained at a systolic pressure of less than 100 mmHg. Use of crystalloids, packed erythrocytes, platelets, and fresh frozen plasma were based on criteria established by protocol. Estimated blood loss was assessed by weighing sponges and measuring suctioned blood from canisters.**

***Results*: Estimated blood loss (intraoperative and postoperative) and amount of packed erythrocytes transfused were similar for the DDAVP and placebo groups. Concentrations of both factor VIIIC and vWF were significantly greater after DDAVP infusion when compared with concentrations after placebo infusion.**

***Conclusions*: In the children who had complex spinal fusion, there was no difference in estimated blood loss between those who received DDAVP and those who received a placebo. Administration of DDAVP significantly increased factor VIIIC and vWF levels. (Key words: Coagulation, blood loss. DDAVP. Central nervous system, cerebral palsy; spinal fusion.)**

DESMOPRESSIN acetate (1-desamino-8-D-arginine vasopressin [DDAVP]) has been shown to reduce blood loss by what is believed to be its vasopressin$_2$ receptor effects[1] when infused before or at the beginning of coronary artery bypass grafting and spinal fusion surgery. It reduces bleeding times in patients with otherwise normal factor concentrations, including those with normal von Willebrand's factor (vWF) concentrations,[2] and it has been found to increase platelet deposition onto vascular subendothelium in *in vitro* experiments.[3] After initial reports that concluded that DDAVP reduced blood loss during cardiac surgery,[4,5] subsequent studies found no beneficial effect.[6–8] The differences in the results were thought to be methodologic because studies that found an effect of DDAVP on blood loss had enrolled patients undergoing complicated cardiac surgery, such as repeated coronary artery bypass surgery and cardiac valve replacements.[4,6] In contrast, DDAVP brought no advantage to patients having uncomplicated cardiac surgery.[7,8]

Evaluation of the utility of DDAVP in pediatric orthopedic surgery has been hampered by similar problems. The first randomized, controlled study examining the use of DDAVP to reduce blood loss in children enrolled patients with differing preoperative illnesses, such as idiopathic scoliosis, scoliosis secondary to cerebral palsy, and scoliosis secondary to muscular dystrophy.

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Surgery varied with the cause of the scoliosis. Blood loss was reduced by 32.5% in patients who received DDAVP compared with those who received a placebo.[9] However, no reduction in blood loss was apparent when DDAVP was used for patients with idiopathic scoliosis having spinal fusion.[10] Children with cerebral palsy and with muscular dystrophy undergo far more involved spinal fusion procedures, such as spinal fusion with a unit rod. This procedure decorticates and fuses the spine from the T1 vertebra to the sacrum and results in a greater amount of blood loss.

Therefore, we designed this study to examine the effect of DDAVP in reducing blood loss in children with scoliosis secondary to cerebral palsy alone. In addition, we examined the ability of DDAVP to increase factor VIIIC and vWF concentrations in children with cerebral palsy and spastic quadriplegia.

Materials and Methods

The project was approved by the Institutional Review Board at the duPont Hospital for Children. Forty patients were to be enrolled in the study; however, at interim data analysis following 21 patients, the Institutional Review Board recommended termination of the study (see Results). Twenty-one patients with cerebral palsy and neuromuscular scoliosis scheduled to undergo spinal fusion with unit rod instrumentation were enrolled in this randomized, controlled study. Parental consent was obtained. All patients satisfied Evan's classification of stage IV cerebral palsy.[11] Exclusion criteria included history of bleeding problems, prolonged prothrombin time (> 13 s), partial thromboplastin time (> 40 s), a bleeding time of longer than 7 min, and thrombocytopenia (platelet count < 150,000). Triceps skinfold thickness was measured by averaging three measurements of skinfold thickness over the triceps area at the midpoint between the acromion and olecranon. Forearm length measurement for height[12] was taken in the preoperative holding room. Each patient received either 0.3 μg/kg DDAVP in 100 ml normal saline (DDAVP group) or 100 ml normal saline alone (placebo group) during a period of 15–20 min while in the preoperative holding room area. The DDAVP solution and the placebo solution were clear and identical in appearance. The surgeon, anesthesiologist, and investigator collecting the experimental data were unaware of which solution was being administered. Blood pressure and heart rate were measured every 5 min during the administration of the study solution.

Anesthetic Management

Before operation, patients received either 500 μg/kg oral midazolam or 2 mg intravenous midazolam after an intravenous catheter was placed. All patients were monitored using a three-lead electrocardiogram, continuous pulse oximetry, a 22-gauge radial artery catheter for measurement of blood pressure, a 9-French central venous catheter placed in the subclavian or internal jugular vein, a Foley catheter to measure urine output, and an esophageal temperature monitor. End-tidal carbon dioxide was monitored, and ventilation was adjusted to achieve an end-tidal carbon dioxide level of 35 to 45 mmHg. A 16- or 18-French nasogastric tube was left in place to keep the stomach decompressed. A Bair hugger (Murat) warming blanket (Augustine Medical, La Praye, Switzerland) was placed on the lower half of the body to keep the patient's temperature between 35 and 36.5°C. All patients were placed prone on a Relton-Hall frame.

Anesthesia consisted of induction with sodium thiopental (3–5 mg/kg), relaxation with vecuronium bromide, isoflurane less than 1% expired (end-tidal), and fentanyl citrate (15–25 μg/kg) to maintain a systolic blood pressure of less than 100 mmHg and heart rate of less than 100 beats/minute. Small doses (5-mg increments) of labetalol were given to control blood pressure as necessary. Three milliliters of normal saline was given for every milliliter of blood loss. All patients received 15–20 ml/kg 5% albumin, which was given empirically after surgery started and before packed erythrocyte transfusion began. The albumin was not considered replacement. When the hemoglobin concentration reached 10 g/dl, packed erythrocyte transfusion was begun. If at any time the anesthesiologist was in doubt about the transfusion of erythrocytes, further hemoglobin estimations were done. Erythrocyte transfusion was continued if hemoglobin was less than 10 g/dl. Hemoglobin concentration was frequently checked to better estimate the extent of the patient's circulating erythrocyte mass. Our goal was an hemoglobin concentration of 10–12 g/dl at the end of surgery. Fresh frozen plasma was transfused if any of the prothrombin time/partial thromboplastin time (PT/PTT) measurements described were prolonged (more than than the upper limit of normal), depending on the stage of surgery at the time and the extent of surgery that was still left to be done. If clinically evident excessive oozing (evidenced by the surgeon's inability to see the operative field because of the pooling of blood) was present, fresh frozen plasma was transfused after drawing a blood sample for PT/

PTT. This criteria was incorporated into the protocol to protect the patient, so the practitioner could initiate transfusion of fresh frozen plasma if it was believed that obtaining PT/PTT results may result in too long of a wait. One unit of platelets per 5 kg body weight was transfused if the platelet count was less than 100,000/ml, again based on the stage of surgery when the platelet count was measured and the extent of surgery still to be done. Platelet measurements were performed at intervals determined by the amount of blood loss (*e.g.*, at blood loss of one blood volume). Blood loss was calculated by weighing sponges and directly measuring blood suctioned from the wound.

Surgical Technique

A surgical incision was made in each patient after the blood sample was drawn for post-drug measurement of factor concentration, 1 h after study drug administration. Subcutaneous tissue was infiltrated with 100–200 ml normal saline with one part per 500,000 dilution of epinephrine. Subperiosteal dissection was performed from the C7 to the S3 vertebrae and included the lateral aspects of both iliac crests. All soft tissue was removed from the lamina, facets, and transverse processes. Complete facetectomies and decortication of the lateral lamina and transverse process were performed from the T1 vertebra to the sacrum. The rod was placed into the holes drilled into the pelvis, sequentially reduced to each lamina, and wired to the lamina. The fascia was closed tightly, and this was followed by subcutaneous and subcuticular skin closure. No drains were used, and the patient was maintained supine for 12 h. During the procedure, the largest amount of blood was lost during decortication, which occurred 2–4 h after the study drug solution was administered.

Postoperative Management

All patients were kept tracheally intubated and admitted to the pediatric intensive care unit. All patients were supported with mechanical ventilation. Patients were weaned off the ventilator beginning on the first postoperative day at the discretion of the pediatric intensive care unit physician. Packed erythrocytes were transfused if the hemoglobin concentration was less than 10 g/dl. Postoperative (the first postoperative day was defined as a duration of 24 h from admission to the pediatric intensive care unit) bleeding was assessed if the dressing became soaked and needed to be changed. If only bloody serous fluid was present, postoperative bleeding was considered insignificant. If the dressing was soaked by blood and need to be changed, then the pediatric intensive care physician estimated the blood loss subjectively.

Measurement of Hematologic and Other Parameters

Concentrations of factor VIIIC, vWF (antigen), PT, and PTT were measured just before infusion of the study solution and 1 h after completion of the study solution. Hemoglobin, platelets, PT, and PTT were measured when packed erythrocyte transfusion began (when the hemoglobin concentration decreased to 10 g/dl), at loss of one blood volume, and at the completion of surgery (on admission to the pediatric intensive care unit). The hemoglobin concentration was measured by the anesthesiologists as often as necessary to guide erythrocyte transfusion. A Foley catheter was placed immediately after induction of general anesthesia, typically within 1 h after administration of the study drug. Urine output was measured every 30 min.

Statistical Analysis

Sample Size Calculation. A sample of 40 patients (20 in each group) was necessary to detect a difference in blood loss equal to 30% of estimated blood volume, given a standard deviation of 100 ml, an alpha coefficient of 0.05, and a power of 0.8.

Interim Data Analysis. An interim analysis was to be done when 20 patients were enrolled to identify any adverse effect from DDAVP, and the study was to be terminated if a significant adverse effect was identified without justifiable benefit.[13] Interim results, as reported here, indicated that the study should be terminated.

Analysis of Data. An examination of standard deviations for both the confounding and dependent variables used in the study revealed that several variables were not normally distributed. Consequently, all group comparisons were completed using nonparametric statistical analyses. Blood pressure and temperature measurements were obtained across time. Therefore data were analyzed using two methods: repeated-measures analysis of variance to account for group X time differences, and Mann-Whitney tests for each set of measurements per time. As shown below, results from the repeated-measures analysis of variance and the individual Mann-Whitney analyses were identical, but with one exception. The Results section emphasizes findings from the Mann-Whitney comparisons, because the blood pressure and temperature measurements were not normally

Table 1. Potentially Confounding Variables

Outcome	DDAVP		Placebo		
	Median	Range	Median	Range	*P* Value*
Age (y)	13.0	10.0–19.0	13.0	6.0–18.0	0.35
Weight (kg)	23.0	14.5–50.0	24.0	18.0–48.0	0.94
Degree of scoliosis	81.0	55.0–110.0	92.0	66.0–100.0	0.72
Preop Hgb (g/dl)	13.3	11.9–15.1	13.2	12.9–14.9	0.95
Postop Hgb (g/dl)	11.4	10.0–11.9	11.6	8.0–12.5	0.75
Preop platelet count (× 1,000/mm^3)	364.0	208.0–409.0	318.0	160.0–396.0	0.23
Duration of surgery (h)	4.5	3.45–5.0	4.3	3.45–5.15	0.25
Amount of labetalol used (mg)	10.0	0–20	12.5	0–25.0	0.85
Lowest temperature recorded during surgery (°C)	35.0	34.6–35.5	35.0	34.4–35.3	0.22

DDAVP = desmopressin acetate; Preop = preoperative; Hgb = hemoglobin.

* By Mann-Whitney test.

distributed. Probability values less than 0.05 were considered significant.

Results

Twenty-one patients were enrolled in the study at interim analysis. All patients had spinal fusion involving the T1 vertebra to the sacrum. All potentially confounding variables are given in table 1. Age, weight, sex, and degree of curvature of the spine were similar for the two groups of patients. Triceps skinfold thicknesses measured to assess patient nutritional status were similar for the two groups ($P = 0.86$ by Mann-Whitney analysis). Long-term anticonvulsants were administered in 13 patients. Valproic acid was being administered to one patient in the DDAVP group and to three patients in the placebo group. Carbamazepine was being given to two patients in each group. Phenobarbital was being administered to four patients in the DDAVP group and to two patients in the placebo group. For some patients, more than one anticonvulsant agent was being given to control seizures. The median of estimated blood loss for the patient receiving valproic acid was 149% for the DDAVP group. The median of estimated blood loss for patients receiving valproic acid in the placebo group was 126%, with a range of 108–239.5%. All but two patients were operated on by the same surgeon. Of the two patients who had a different surgeon, one patient was in the placebo group and the other was in the DDAVP group. The patient in the placebo group had an estimated blood loss of 65% of estimated blood volume, whereas the patient in the DDAVP group had an estimated blood loss of 158% of estimated blood volume. Analysis of estimated blood loss for the two groups with these two cases excluded showed similar results ($P = 0.37$) by the Mann-Whitney test.

The following confounding variables were measured at multiple times. The groups were compared using repeated-measures analysis of variance to account for group X time differences, and Mann-Whitney tests were used for each set of measurements per time. Results from the repeated-measures analysis of variance showed that intraoperative temperature measurements ($P = 0.70$), heart rate measurements ($P = 0.53$), systolic ($P = 0.41$), mean blood pressure measurements ($P = 0.14$), and isoflurane concentrations ($P = 0.89$) were not different for the groups. These findings were further analyzed using multiple Mann-Whitney tests for each set of measurements per time period. The only significant difference observed was in the mean blood pressure 15 min after the beginning of surgery, when the placebo group ranked higher than the DDAVP group. During the first hour of surgery, it was more difficult to maintain a heart rate less than 100 beats/min. Patients received most of the labetalol during this time. The amount of labetalol used was not different ($P = 0.85$) between the groups.

Preoperative hemoglobin concentration, hemoglobin concentration at admission to the pediatric intensive care unit, preoperative platelet count, and surgery duration were similar for both groups (table 1). No patient in either group was obese, which is defined as a body mass index (weight measured in kilograms per height in square meters) greater than 30. Nutritional parameters

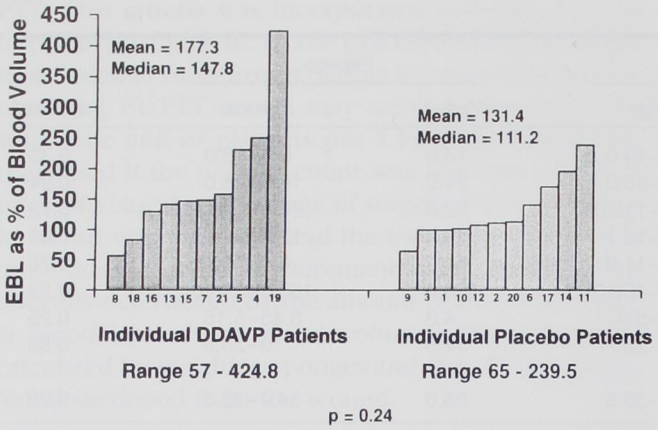

Fig. 1. Estimated blood loss in patients enrolled in the study calculated as a percentage of estimated blood volume (*P* value calculated according to the Mann-Whitney U test).

were measured by triceps skinfold thickness and body mass index criteria. All but four patients were below the 50th percentile for triceps skinfold thickness. Two patients in each group were between the 50th and 75th percentiles. Estimated blood loss for the two patients in the DDAVP group was 57.4% and 130%, and estimated blood loss for the two patients in the placebo group was 111.2% and 141%.

There was no difference in estimated blood loss (calculated as a percentage of the patient's estimated blood volume), analyzed by Mann-Whitney test for nonparametric analysis, between the groups (fig. 1). Not only was there no difference in blood loss between groups but the outcome was contrary to expectations, because the patients who received DDAVP had uniformly larger amounts of estimated blood loss (fig. 1). The 95% confidence interval for the differences in blood loss is −120 to 28. The negative value indicates that the DDAVP was less effective than the placebo. Thus the insignificant difference and the contrary finding that suggested that DDAVP was not efficacious in reducing blood loss prompted us to perform a *post hoc* power analysis to determine if a larger sample might change the findings. An effect size of 0.08 resulting from the power analysis indicated that a statistically significant difference would not occur even if the study continued and enrolled the original study design of 40 patients. Consequently, the study was terminated and the results are reported for the original interim sample of 21 patients.

The amount of packed erythrocytes transfused was similar for both groups during surgery and the first postoperative 24 h (table 2). No patient needed a dressing change for postoperative bleeding, and thus postoperative bleeding was considered insignificant for all patients. Factor VIIIC and vWF concentrations were significantly greater ($P = 0.011$ and $P = 0.0074$, respectively) in the DDAVP group when compared with the placebo group by Mann-Whitney test (table 2). When change in PTT before and after DDAVP administration was compared with change in PTT before and after placebo administration, a significant ($P = 0.0049$) decrease in PTT was seen after DDAVP administration only (table 3).

Two patients in the placebo group had a lower (27 and 45) than normal range (50–150% of normal) of factor VIIIC concentration before infusion of the study solution. The first patient's factor VIIIC concentration increased to 68 after the placebo infusion, whereas the second patient's concentration remained the same after placebo infusion. Von Willebrand's factor concentration was less than normal range (50–150% of normal) in two patients in the DDAVP group before DDAVP infusion, and it increased to normal (39–71, 30–105) 1 h after infusion.

In two patients who received DDAVP, blood pressure decreased during the infusion (one from 94/51 mmHg to 61/40 mmHg, the other from 102/68 mmHg to 74/38 mmHg). The effect was transient, and no change was made in the infusion. Urine output was not significantly different between the two groups (table 3).

Discussion

Desmopressin acetate is efficacious in the management of hemophilia and von Willebrand's disease.[14–16] This proved efficacy of DDAVP prompted examination of its possible effects on reducing blood loss in surgeries that involve substantial blood loss, such as coronary artery bypass grafting, hip surgery, and spinal fusion. However, the studies have varied methodologically in sample size, end points, statistical power, and, therefore, in the evidence provided to support their conclusions.

Our study enrolled a homogenous group of patients, namely children with spastic cerebral palsy and severe scoliosis undergoing only one type of surgical correction: unit rod insertion. Unit rod insertion is a surgical procedure that fuses the spine from the T1 vertebra to the sacrum and is surgically more extensive than the Harrington rod or Luke rod procedures performed for neuromuscular scoliosis.

Table 2. Estimated Blood Loss, Packed Red Cells Transfused, and Factor Levels between DDAVP and Placebo Groups

Outcome	DDAVP		Placebo		
	Median	Range	Median	Range	*P* Value*
EBL (as % of patient's BV) 24 h	147.8	57.0–424.8	111.2	65.0–239.5	0.24
PRBC given in OR (ml/kg)	51.5	24.0–98.6	48.3	24.5–96	0.67
PRBC given in PICU (ml/kg)	13.5	0–32.9	15.3	0–24.0	0.86
PRBC given total (ml/kg)	64.8	30.3–123.6	64.9	33.8–110	0.67
Factor VIIIC before drug infusion†	72.0	52.0–95.0	84.0	27.0–115.0	0.60
Factor VIIIC after drug infusion†	100.0	66.0–235.0	64.0	45.0–120.0	0.011
Factor VIII vWF before drug infusion†	91.0	30.0–313.0	94.0	67.0–239.0	0.55
Factor VIII vWF after drug infusion†	104.0	71.0–245.0	88.0	76.0–137.0	0.0074

DDAVP = desmopressin acetate; EBL = estimated blood loss; BV = blood volume; PRBC = packed red cells; vWF = von Willebrand's factor; OR = operating room.

* By Mann-Whitney test.

† Factor levels expressed as percentage of normal. Normal is 50% to 150% of mean activity of a nondiseased reference population.

Cerebral palsy and lifelong spasticity render these children nonambulatory with lean body habitus. Our clinical experience has been that children with cerebral palsy and spasticity have greater blood loss (not explained by the more extensive nature of the surgery alone) than do healthy children undergoing spinal fusion for idiopathic scoliosis. Our bias had been that their preoperative physical status possibly caused unknown difficulties with intrinsic and vascular homeostatic properties. Yet, similar to Guay *et al.*'s study, in which DDAVP made no difference in estimated blood loss in otherwise healthy children with idiopathic scoliosis,[10] DDAVP made no difference in estimated blood loss in children with cerebral palsy.

Factor VIII procoagulant and vWF concentrations are increased in children with cerebral palsy in response to DDAVP. Factor VIII is a labile factor and an acute-phase reactant. As such it is subject to change with

Table 3. Hematologic Parameters and Urinary Output between DDAVP and Placebo Groups

Outcome (pre- to postdrug)	DDAVP		Placebo		
	Median	Range	Median	Range	*P* Value*
Δ in PTT (pre- to postdrug) (s)	1.50	−3.0–41.0	−3.5	−5.0–1.0	0.0049
Δ in PT (pre- to postdrug) (s)	0.50	1.6–(−0.10)	−0.60	−2.0–0.10	0.96
PTT at transfusion of red cells (s)	46.0	30.0–62.0	33.5	27.0–55.0	0.054
PT at transfusion of red cells (s)	14.0	11.6–15.5	13.8	12.7–16.8	0.77
PTT at EBL of one BV (s)	47.5	40.0–88.0	40.5	34.0–79.0	0.072
PT at EBL of one BV (s)	16.0	15.5–19.6	15.2	14.0–20.0	0.19
PTT in ICU (s)	44.5	34.0–91.0	36.0	28–69.0	0.040
PT in ICU (s)	16.0	11.4–28	15.8	13.6–16.9	0.56
Platelet at PRBC transfusion (× 1,000/mm^3)	243.0	154.0–371.0	234.0	120.0–253.0	0.27
Platelet at EBL of one BV (× 1,000/mm^3)	142.0	118.0–154.0	128.0	61.0–234.0	0.91
Platelet in ICU (× 1,000/mm^3)	105.00	46.0–134.0	122.0	63–271	0.14
U/O first 2 h† (ml · kg^{-1} · h^{-1})	0.10	0–0.5	0.28	0.06–1.52	0.057
U/O first 4 h† (ml · kg^{-1} · h^{-1})	0.75	0–3.7	1.1	0.20–5.1	0.91
U/O first 24 h† (ml · kg^{-1} · h^{-1})	2.7	1.3–5.4	2.1	0.53–8.3	0.31

Laboratory normals for PT = 10–13 s; Laboratory normals for PTT = 26–40 s; ΔPT/PTT = prestudy drug measurements (measurements 1 h after study drug administration); DDAVP = desmopressin acetate; PT = prothrombin time; PTT = partial thromboplastin time; EBL = estimated blood loss; BV = blood volume; U/O = urine output; ICU = on admission to intensive care unit.

* By Mann-Whitney test.

† Time measured from the time of Foley catheter replacement.

extrinsic factors such as anesthesia and catecholamine release.[17] This would explain the variability prevalent in the ability of DDAVP to increase factor VIII procoagulant and vWF concentrations in different studies.[18] We measured the factor concentrations before incision to decrease the extraneous influences placed on the concentrations (catecholamine-induced increase in factor VIII).

There were nine patients with prolonged (greater than upper limit of normal range) PT/PTT with a blood loss of only 10–15% of their estimated blood volume. This was unexpected, because in healthy patients, prolongation of PT/PTT would not be expected at such an early stage during blood loss.[19] We cannot explain this, and any postulation made will be unfounded on objective information.

Patients in our study did not need intervention for decreased urine output, as was the case in other studies.[6,9] A mild decrease in blood pressure was seen in two patients during DDAVP infusion. No intervention was made to correct the hypotension, which corrected itself within 5 min. A more significant and severe decrease in blood pressure occurred when DDAVP was administered to patients completing cardiopulmonary bypass under the influence of general anesthesia.[13]

The effect on platelet count and volume has been inconsistent among the studies mentioned. Patients in Salzman *et al.*'s study had a significantly higher platelet count 90 min after DDAVP administration when compared with patients who received a placebo.[4] Hedderich *et al.*'s study showed a lower platelet count after operation in patients who received DDAVP,[8] and Kobrinski *et al.*'s study found that the platelet volume and platelet count were significantly lower in patients who received DDAVP when compared with those who received a placebo.[9] In addition to absolute platelet count, aggregatory response to adenosine-diphosphate and ristocetin in response to DDAVP has varied among studies.[20] The only disease for which a specific abnormality in platelet aggregation and count has been determined is type IIB von Willebrand's disease. Unlike other types of von Willebrand's disease, type IIB is associated with abnormal platelet aggregation and marked thrombocytopenia in response to DDAVP.[21] We did not find abnormal platelet counts as a result of DDAVP administration in our patients with cerebral palsy.

Epinephrine used by our surgeons to induce vasoconstriction before skin incision could cause platelets to adhere to the vascular endothelium, thus confounding the effect of DDAVP on platelets.[22] Barnhart had shown that, *in vitro*, platelet adhesion to the vascular endothelium with DDAVP pretreatment was significantly greater than with epinephrine pretreatment.[3] We do believe the effect of epinephrine on platelet aggregation was negligent in this study.

Valproic acid (an anticonvulsant) has been shown to cause thrombocytopenia and hypofibrinogenemia.[23] A state similar to Von Willebrand's disease type 1, in which factor VIIIC, vWF, and ristocetin-cofactor were all decreased, has been noted in some patients treated with valproic acid.[24] The number of patients in each group receiving valproic acid was too small to analyze separately their estimated blood loss.

Plasma concentrations of tissue plasminogen activator increase after administration of DDAVP. But Horrow *et al.*[25] found that administering an antifibrinolytic agent, thus negating the effect of tissue plasminogen activator, did not affect DDAVP's lack of hemostatic effect in patients having cardiac surgery. Prostacyclin$_2$, a potent antiplatelet agent that would counteract the aggregating effect of factor VIII, is released by DDAVP and may be another contributing factor to DDAVP's lack of efficacy in reducing blood loss.[26]

The dose of DDAVP used here was based on an observed plateau of factor VIIIC dose response in healthy persons at 0.30 μg/kg when incremental doses of 0.10–0.40 μg/kg were used.[27] This dose has been widely used in studies in which DDAVP had been thought to be effective in reducing blood loss.[4,6]

In conclusion, during spinal fusion using a unit rod in children with severe cerebral palsy, there was no difference in estimated blood loss and amount of blood transfused in those who received DDAVP compared with those who received a placebo.

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