Hemostatic and Fibrinolytic Response to Nasal Desmopressin in Hemodialysis Patients

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Key Words

Nasal desmopressin · Hemodialysis patients · Hemostasis

Abstract

Objective: To evaluate the effect of desmopressin (DDAVP) on hemostatic parameters during dialysis and in the interval between dialysis sessions. **Subjects and Methods:** Fifteen patients dialyzed twice weekly at least for 1 year and 15 healthy volunteers serving as a control group were enrolled in the study. Bleeding time, platelet count, prothrombin time, activated partial thromboplastin time, tissue plasminogen activator (tPA), plasminogen activator inhibitor (PAI-1), euglobulin clot lysis time, protein C, protein S, fibrinogen, D-dimer, factor V, VII, VIII, IX, X and von Willebrand factor (VWF) values were studied at the beginning, at 2 and 4 h of dialysis with and without administration of DDAVP at a dose level of 2 µg/kg intranasally. **Results:** After dialysis, bleeding time shortened, PAI-1 and fibrinogen levels were lower, while VWF and D-dimer levels were higher. After DDAVP administration, bleeding time, PAI-1 levels were significantly lower ($p < 0.01$), while tPA, factor VIII and VWF levels increased significantly ($p < 0.001$). **Conclusion:** The findings indicate that DDAVP can be used for patients on dialysis with serious bleeding.

Introduction

Frequently, there is a tendency for bleeding to occur in the later periods of chronic renal failure (CRF); especially gastrointestinal and intracranial bleeding may be serious in some of these patients [1, 2]. Although modern therapeutic methods for the treatment of uremia can reduce serious bleeding episodes significantly, bleeding is still one of the basic problems. Dialysis does not improve platelet dysfunction completely [3]. Recently some studies have shown that desmopressin (DDAVP) could be used in bleeding patients with CRF [4, 5] during hemodialysis because DDAVP reduces the level of protein C [6], increases the level of factor VIII and von Willebrand factor (VWF), while DDAVP raises tissue plasminogen activator (tPA) and lowers tissue plasminogen activator inhibitor (PAI-1) [7, 8]. Few studies have been done on the administration of DDAVP to patients on chronic hemodialysis treatment, involving hemostatic parameters [4].

In this study, we have assessed the effect of nasal DDAVP on hemostatic parameters of patients on chronic hemodialysis treatment, during and in the interval between dialysis sessions.

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Table 1. Hematologic findings of patients with CRF and a healthy control group

Parameters	Normal ranges	1Patients	1Controls	p value
Bleeding time, min	2–5	5.8 ± 1.9	4.0 ± 0.5	<0.01
Platelet, × 10 ⁹	1.5–4.0	2.0 ± 0.6	2.7 ± 0.3	<0.001
PT, s	10–14	13.40 ± 0.6	13.53 ± 0.8	NS
aPTT, s	26–40	30.7 ± 5.5	28.5 ± 2.2	NS
tPA, ng/ml	3–10	10.0 ± 4.3	9.2 ± 2.5	NS
PAI-1, ng/ml	4–43	35.57 ± 5.18	44.14 ± 10.79	<0.01
ECLT, min	90–240	225.3 ± 44.0	201.4 ± 29.8	NS
Protein C, IU/ml	0.59–1.37	1.14 ± 0.36	1.45 ± 0.41	<0.05
Protein S, %	73–151	87 ± 27	114 ± 12	<0.01
Fibrinogen, mg/dl	160–350	626.2 ± 200.3	391.2 ± 97.0	<0.05
D-dimer, µg/ml	0.0–0.5	0.32 ± 0.17	0.37 ± 0.16	NS
Factor V, %	40–150	36 ± 15	65 ± 22	<0.001
Factor VII, %	40–150	98 ± 34	151 ± 47	<0.01
Factor VIII, %	40–150	71 ± 12	77 ± 5	NS
VWF, %	40–150	88 ± 3	83 ± 11	NS
Factor IX, %	40–150	62 ± 55	60 ± 11	NS
Factor X, %	40–150	119 ± 29	122 ± 23	NS

NS = Nonsignificant. Results are given as means ± SD.

Subjects and Methods

Fifteen patients (9 men and 6 women) dialyzed with bicarbonate dialysate twice weekly at least for 1 year and 15 healthy volunteers (10 men and 5 women) as control were included in this study. No significant bleeding episodes were present in the patients' follow-up. Patients were given a loading dose of 1,000 U of heparin at the beginning and 500 U per hour during dialysis.

Average age was 45 ± 13 and 48 ± 8 years in CRF and controls, respectively. The patients did not receive anticoagulant or antiaggregant agents except heparin during dialysis. In the first stage of the study, blood samples (as 1/10 ratio citrated blood) were taken from both groups, bleeding time was measured using Duke's method, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), tPA, PAI-1, euglobulin clot lysis time (ECLT), protein C, protein S, fibrinogen, D-dimer, factor V, VII, VIII, IX, X and VWF values were also measured.

In the second stage, at the onset of hemodialysis, at 2 and 4 h the same parameters were measured again in the study group. In the third stage, the patients received 2 µg/kg Ferrin AB 'Minirin' nasal spray (DDAVP) intranasally at the beginning of the dialysis session and the same parameters were remeasured. No atrophy of the nasal mucosa was observed in patient and control groups. In the last stage, the patients received 2 µg/kg DDAVP in the intervals between the dialysis sessions (36 h after dialysis) and the same parameters were measured 4 h later. The kits used were Organon Simplastin excel kit for PT, Organon Automated kit with coagulometer for aPTT, Biopool tint ELISA tPA kit for tPA, Biopool Spectrolyse/PL PAI kit (by chromogenic method) for PAI-1, Organon Fibriquick kit (by coagulometric method) for fibrinogen level, Biopool Minutex™ D-dimer kit for D-dimer calculation, Stage As-serachrom VWF kit for VWF (by ELISA method). Protein C and S were measured by ELISA method, factor levels were measured by coagulometric method with an Organon factor-deficient kit.

Statistical analysis between the two groups was compared using Student's t test (for small samples); Wilcoxon Rank Order test was used in the study group. Results were given as means ± SD, and $p < 0.05$ was considered statistically significant.

Results

Significant clinical bleeding or thrombotic episodes were not observed in the patients. The baseline hemostatic parameters of both study and control groups are given in table 1.

Bleeding time in the study group was significantly longer ($p < 0.01$) than that of controls. Platelet counts were lower ($p < 0.01$) but fibrinogen was higher ($p < 0.05$) in the study group than in the controls. In addition, protein C ($p < 0.05$), protein S ($p < 0.01$), PAI-1 ($p < 0.01$), factor V ($p < 0.001$) and factor VII ($p < 0.01$) levels were also significantly lower in the study group than the control group. There was no significant difference in other hemostatic parameters of both study and control groups (table 1).

The hemostatic parameters for the second part of the study, evaluated at the beginning, at 2 and 4 h of dialysis are given in table 2. Bleeding time was significantly shorter ($p < 0.05$) 4 h of dialysis than at the beginning. The aPTT values were longer after 4 h of dialysis ($p < 0.001$). However, the level of PAI-1 was shorter at 4 h of dialysis ($p < 0.05$). Fibrinogen levels were lower ($p < 0.05$), whereas VWF ($p < 0.05$) and D-dimer levels were higher ($p <$

Fig. 1. Bleeding time of patient group and healthy control group.

Fig. 2. D-dimer levels of patient group during hemodialysis.

Table 2. Hematologic findings in patients with CRF during hemodialysis

	1A1	1A2	1A3	A1-A3
Bleeding time, min	6.00 ± 2.14	4.28 ± 1.12	4.67 ± 1.61	p < 0.05
Platelet count, × 10 ⁹	2.0 ± 0.7	2.0 ± 0.7	2.0 ± 0.8	NS
PT, s	13.50 ± 1.32	14.21 ± 0.84	14.62 ± 1.57	NS
aPTT, s	30.50 ± 2.82	100.55 ± 44.12	102.52 ± 40.98	p < 0.001
tPA, ng/ml	12.53 ± 5.45	15.67 ± 6.70	12.89 ± 5.33	NS
PAI-1, ng/ml	32.50 ± 7.00	26.35 ± 6.88	25.28 ± 6.86	p < 0.05
ECLT, min	184.28 ± 59.28	181.07 ± 56.06	181.07 ± 42.70	NS
Protein C, IU/ml	1.00 ± 0.25	1.07 ± 0.21	1.05 ± 0.25	NS
Protein S, %	75 ± 29	72 ± 19	75 ± 33	NS
Fibrinogen, mg/dl	591.80 ± 190.10	473.40 ± 142.50	470.20 ± 100.80	p < 0.05
D-dimer, µg/dl	0.42 ± 0.13	0.52 ± 0.10	0.66 ± 0.15	p < 0.05
Factor V, %	36 ± 11	42 ± 23	44 ± 17	NS
Factor VII, %	84 ± 27	82 ± 24	84 ± 29	NS
Factor VIII, %	91 ± 17	87 ± 17	90 ± 14	NS
VWF, %	93 ± 42	96 ± 41	101 ± 43	p < 0.05
Factor IX, %	62 ± 20	58 ± 14	59 ± 21	NS
Factor X, %	127 ± 40	122 ± 36	114 ± 41	NS

A1 = First value; A2 = 2 h; A3 = 4 h; NS = not significant.

0.05) at 4 h than at the beginning of dialysis. The other hemostatic values showed no significant difference before and during dialysis.

After DDAVP administration, bleeding time and PAI-1 levels were significantly lower ($p < 0.001$), but aPTT ($p < 0.01$) and tPA ($p < 0.05$) levels increased significantly. Factor VIII and VWF levels increased significantly ($p < 0.05$ and $p < 0.01$, respectively) at 4 h of dialysis (table 3). Other parameters showed no difference following DDAVP administration at 4 h of dialysis.

For the final step of the study, bleeding time was shorter ($p < 0.001$), aPTT levels decreased ($p < 0.01$), tPA values ($p < 0.001$), factor V ($p < 0.001$), factor VIII ($p < 0.001$), VWF ($p < 0.001$), factor IX ($p < 0.01$) and VWF ($p < 0.001$) levels significantly increased (table 3). On the other hand, the protein C level ($p < 0.01$) and ECLT ($p < 0.001$) decreased significantly. The other parameters did not change significantly 4 h later.

Fig. 3. Fibrinogen levels of the patient group during hemodialysis.

Fig. 4. Bleeding time (min) of the patient group after DDAVP during hemodialysis (interrupted line) and in the interval between hemodialysis sessions (solid line).

Table 3. Hematologic findings in patients with CRF during dialysis and in the interval between dialysis sessions after DDAVP nasal administration

	A1d	A2d	A3d	A1de	A2de	A3de	A1d A3d	A1de A3de
Bleeding time, min	6.60 ± 2.41	3.78 ± 1.51	2.64 ± 1.39	5.85 ± 1.95	3.71 ± 1.14	2.82 ± 1.30	p < 0.001	p < 0.001
Platelets/min	2.1 ± 0.8	2.3 ± 0.7	2.1 ± 0.7	2.0 ± 0.7	1.9 ± 0.7	2.0 ± 0.7	NS	NS
PT, s	13.45 ± 1.00	14.18 ± 1.51	14.00 ± 0.98	13.40 ± 0.63	13.03 ± 0.96	13.01 ± 1.12	NS	NS
aPTT, s	34.20 ± 4.61	92.23 ± 38.13	95.62 ± 32.17	30.71 ± 4.56	30.20 ± 5.77	28.50 ± 5.55	p < 0.01	p < 0.01
tPA, ng/ml	12.39 ± 4.42	17.85 ± 7.40	17.64 ± 8.24	10.03 ± 4.39	15.53 ± 6.15	19.53 ± 10.98	p < 0.05	p < 0.001
PAI-1, ng/ml	34.78 ± 3.68	20.42 ± 4.48	15.00 ± 4.44	35.57 ± 5.18	28.57 ± 9.10	23.92 ± 11.33	p < 0.001	p < 0.01
ECLT, min	287.50 ± 52.00	181.78 ± 55.00	161.00 ± 50.65	225.35 ± 44.84	195.00 ± 47.85	162.85 ± 41.00	NS	p < 0.001
Protein C, IU/ml	1.21 ± 0.35	1.02 ± 0.35	0.87 ± 0.23	1.14 ± 0.36	0.83 ± 0.30	0.71 ± 0.30	NS	p < 0.01
Protein S, %	60 ± 29	68 ± 41	67 ± 38	87 ± 27	86 ± 33	81 ± 32	NS	NS
Fibrinogen, mg/dl	624.50 ± 100.70	624.80 ± 154.30	541.60 ± 152.00	626.20 ± 200.00	573.40 ± 262.68	398.60 ± 164.30	NS	p < 0.01
D-dimer, µg/dl	0.42 ± 0.18	0.49 ± 0.15	0.65 ± 0.11	0.42 ± 0.15	0.39 ± 0.10	NS	NS	NS
Factor V, %	40 ± 18	41 ± 12	44 ± 15	36 ± 15	51 ± 21	52 ± 21	NS	p < 0.001
Factor VII, %	91 ± 47	84 ± 21	86 ± 19	98 ± 34	107 ± 45	186 ± 26	NS	NS
Factor VIII, %	82 ± 24	123 ± 81	146 ± 37	71 ± 12	134 ± 46	140 ± 27	p < 0.05	p < 0.001
VWF, %	86 ± 41	107 ± 12	128 ± 15	88 ± 37	104 ± 44	131 ± 45	p < 0.01	p < 0.001
Factor IX, %	53 ± 19	68 ± 21	69 ± 26	62 ± 25	77 ± 33	72 ± 30	NS	p < 0.01
Factor X, %	116 ± 41	112 ± 34	117 ± 33	119 ± 29	110 ± 30	118 ± 32	NS	NS

A1d = First value during hemodialysis; A2d = at 2 h during dialysis after DDAVP; A3d = at 4 h during dialysis after DDAVP; A1de = first value in the interval between dialysis sessions; A2de = 2 h after a dialysis session (interval); A3de = 4 h after a dialysis session (interval).

Fig. 5. VWF levels (%) of the patient group after DDAVP during hemodialysis (interrupted line) and in the interval between hemodialysis sessions (solid line).

Discussion

In patients with CRF, hemostatic disorders such as bleeding diathesis and hypercoagulability may occur [9], probably due to an increase in prostacyclin levels compared to thromboxane A₂, aggregation and adhesion deficiencies of platelets as it has been shown that platelet count and factor VIII and VWF levels in CRF patients were lower than those of healthy people [10, 11]. In this study, platelet counts were similarly lower, and bleeding time longer in CRF patients than in healthy controls probably due to uremia-related decreased platelet counts and functional alterations in uremic patients [12]. Reduced platelet counts were not below the normal range and therefore could not explain the prolonged bleeding time. It is possible that the decreased platelet count in CRF patients compared to controls might be due to the use of heparin administered during dialysis as previously reported by Charvat et al. [13]. Also of importance is the decreased level of factor V released from platelets in the patient group, which may be due directly to decreased platelet count and dysfunctional platelet.

Increased levels of fibrinogen in patients may be evidence of suppression of fibrinolysis due to uremic retention [14]. Although PAI-1 level was lower in patients with CRF than in controls, this decrease was not considered to be significant ($p > 0.05$). The other fibrinolytic activity

parameters (tPA and D-dimer levels) did not show any difference between patient and control groups.

Decreased bleeding time after 4 h of hemodialysis indicated the positive effect of dialysis on platelet functions [15, 16]. Also, aPTT was longer due to heparin administration as expected. The fibrinogen level decreased significantly at 4 h of dialysis probably due to an increment of tPA by hemodialysis or the aggregation of fibrinogen on the dialysis membrane [8]. The increment of tPA and D-dimer and the decrease of PAI-1 were thought to be due to the increase in fibrinolysis. The level of VWF at 4 h of hemodialysis was higher than the initial level due to secretion of VWF from endothelium and activated platelets [17, 18], which resulted from endothelial damage and normalization of platelet functions during dialysis. We did not observe any difference in the other hemostatic parameters of blood.

After the administration of DDAVP to the patients at the beginning of hemodialysis, bleeding time shortened as previously reported [6, 9, 12–16]. The shortening of bleeding time with DDAVP might be related to the effect of DDAVP on platelet function, serotonin release, thromboxane A₂ and VWF release, factor VIII ristocetin cofactor activity, and factor VIII-c activity [2, 5, 6, 19, 20]. Although it has been shown that hemodialysis does not affect factor VIII level [4], apparently with administration of DDAVP, factor VIII level increased as previously noted [4, 6].

The increment of tPA at 4h during dialysis was much higher with than without DDAVP administration. These results are in concordance with the studies by Takahashi and Levi [7, 8], which showed that DDAVP raised tPA level. In CRF, this effect is important in the reduction of thromboembolic incidents due to a decrease in fibrinolysis. Other parameters did not show significant changes after the administration of DDAVP during hemodialysis.

Bleeding time and aPTT were also decreased with the administration of DDAVP in the intervals between dialysis sessions. These results paralleled the increment of factor VIII, factor V, factor IX and VWF after DDAVP administration in the interval between dialysis sessions. The levels of PAI-1 and fibrinogen decreased while those of tPA and D-dimer increased. Both ECLT and protein C levels were decreased after DDAVP. These results are in agreement with previous studies [4, 7, 8, 21, 22] and these findings may suggest that DDAVP may also increase fibrinolysis in the intervals between dialysis sessions.

Conclusion

Patients with CRF have a tendency to bleed more during hemodialysis due to the use of heparin. Bleeding can be controlled with the administration of DDAVP, which

shortens bleeding time, increases VWF, factor VIII, factor V and factor IX, despite the increasing effect of DDAVP on fibrinolysis. No adverse effects were observed by the nasal application of DDAVP.

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