EFFECT OF REPEATED ADMINISTRATION OF ε-AMINOCAPROIC ACID ON RECOVERY OF BLOOD VOLUME AND PROTEIN COMPOSITION IN THE EARLY PERIOD AFTER ACUTE BLOOD LOSS IN DOGS

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Experiments on dogs show that ε-aminocaproic acid has no effect on restoration of the volume or protein composition of the plasma after acute blood loss. The results of these experiments do not support the view that a fibrin layer is present on the inner surface of the endothelium and basement membranes of the vessels which plays a significant role in vascular permeability.

The view has recently been expressed [4, 5] that a permanent fibrin layer is present on the inner surfaces of the endothelium and basement membrane of blood vessels, is constantly being renewed through the formation of fibrin and fibrinolysis, and has a marked effect on vascular permeability. There is no direct experimental evidence to support this view, and the indirect evidence [2, 3, 8, 9] is against it.

In a previous investigation the writer [1] showed that the intensity of development of toxic edema of the lungs and the rate of transcapillary passage of water and proteins from the blood into pulmonary edema fluid and from the tissues into the blood are identical in dogs receiving and not receiving ε-aminocaproic acid (ε-ACA).

In the present investigation the effect of ε-ACA on restoration of the circulating plasma volume and the concentrations of proteins circulating in the vascular system was investigated in the early stages after acute blood loss.

EXPERIMENTAL METHOD

Experiments were carried out on two groups of dogs (8 animals in each group) of both sexes, weighing 7-31 kg. One group of dogs received ε-ACA (200 mg/kg, 3 times a day) for 4 days in meat pellets. In this dose, ε-ACA sharply inhibits fibrinolytic activity of the blood [7]. The other group of animals received no ε-ACA and acted as the control.

In the dogs of both groups, before bleeding (25% of the blood volume from the femoral artery), and 60 and 120 min thereafter, the volumes of circulating blood (CBV), plasma (CPV), and erythrocytes (CEV), and the content (CPC) and concentration of total protein in the plasma and the hematocrit index (HI) of the blood were determined.

The CBV was determined from the degree of dilution of intravenously injected homologous erythrocytes labeled with P^{32}. During determination of CBV 60 and 120 min after blood loss, the number of labeled erythrocytes removed during bleeding was subtracted from the total number injected before blood loss. HI of the blood was determined with a hematocrit (3000 rpm for 30-40 min), the total protein concentration

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TABLE 1. Effect of ε-ACA on Passage of Fluid and Protein into Vascular System after Acute Blood Loss in Dogs

	Without ε-ACA				With ε-ACA			
	removed	entered			removed	entered		
		0–60 min	60–120 min	0–120 min		0–60 min	60–120 min	0–120 min
Fluid (in ml/kg)	12,2	8,6	5,5	13,8	12,4	8,7	4,5	13,2
Protein (in g/kg)	0,85	0,32*	0,19*	0,51*	0,85	0,34*	0,14*	0,48*

*P < 0.05 compared with results before blood loss.

Note. In Tables 1 and 2, differences between experimental and control groups are not statistically significant, and values of m are therefore not given in the tables.

TABLE 2. Effect of ε-ACA on Recovery of Serum Protein Composition after Acute Blood Loss in Dogs

	Before blood loss	Expected quantity remaining	Found after 60 min	Found after 120 min
Without ε-ACA				
Albumin (in g/kg)	1,70	1,27	1,54	1,81
Globulins (in g/kg)				
α_1	0,12	0,09	0,09	0,07
α_2	0,24	0,18	0,15	0,13
α_3	0,26	0,19	0,15	0,18
β_1	0,35	0,26	0,28	0,29
β_2	0,51	0,38	0,40	0,35
γ	0,33	0,25	0,35	0,34
A/G ratio	0,94	0,94	1,08	1,33
With ε-ACA				
Albumin (in g/kg)	1,62	1,21	1,46	1,74
Globulins (in g/kg)				
α_1	0,10	0,08	0,09	0,08
α_2	0,15	0,11	0,14	0,10
α_3	0,24	0,18	0,19	0,20
β_1	0,32	0,24	0,32	0,29
β_2	0,50	0,37	0,33	0,35
γ	0,41	0,31	0,31	0,27
A/G ratio	0,94	0,94	1,06	1,35

in the plasma by the IRF-22 refractometer, and CPV and CEV were calculated from the values of CBV and HI. The relative proportions of protein fractions in the serum was determined by paper electrophoresis, using veronal-medinal buffer (pH 8.6, $\mu = 0.1$). CPC and the content of protein fractions in the serum (CPF) were calculated from the values of CPV and the concentrations of total protein in the plasma and protein fractions in the blood serum.

The absolute quantities of water and proteins passing from the tissues into the vascular system were calculated from the difference between values of CPV and CPC actually found 60 to 120 min after bleeding and their expected contents left in the vascular system after removal of 25% of the blood volume.

EXPERIMENTAL RESULTS

In both groups of dogs, the values of CBV, CPC, and the total protein concentration in the plasma were not restored 60 min after the beginning of bleeding, while CPV and HI of the blood were indistinguishable from their initial values. A significant recovery of CBV, a small but not significant increase in CPV, and a decrease in HI of the blood and in the total protein concentration in the plasma were found 120 min after the beginning of bleeding. CPC had not yet regained its initial value.

The calculations showed (Table 1) that in the course of 60 min after bleeding, 38% of protein and 70% of fluid relative to the quantities removed by bleeding passed from the tissues into the vascular system of the control animals. The corresponding figures for the experimental dogs were 40 and 70%. In the course of 120 min, 60% of protein and 113% of fluid entered the vascular system of the control animals, compared with 56 and 106% for the experimental animals. The differences between these values in the control and experimental animals were not statistically significant. Differences between the content of individual protein fractions in the vascular system 60 and 120 min after bleeding likewise were not significant (Table 2).

The results thus show that preliminary and repeated administration of ε-ACA to dogs had practically no effect on restoration or redistribution of fluid and protein in the body in the early stages after acute blood loss.

The present experiments were carried out under conditions of rapid compensatory passage of water and proteins from the tissue fluid into the vascular system. The state of the membranes and, in particular, the state of the hypothetical fibrin layer must have some influence on the rate of transcapillary passage of water and proteins, which is known to take place by diffusion and ultrafiltration. In the present experiments the conditions were favorable to preservation and growth of the fibrin layer on the inner surface of the endothelium and basement membranes of the blood vessels, because prolonged and repeated administration of large doses of ε-ACA prevented fibrinolysis. Selective tests of the efficacy of the dose of ε-ACA used in these experiments showed that 2 and 3 h after administration of a single dose of ε-ACA the fibrinolytic activity of the blood (determined by the euglobulin method [6]) was reduced to between 33 and 50% of its initial value. Because of the rapid breakdown of fibrinogen in dogs (half of it is broken down in 2.4 days [7]), administration of ε-ACA for 4 days can be regarded as sufficient. However, no differences were found between the recovery of CPV and CPC or in the transcapillary passage of fluid and proteins from the tissues into the blood after blood loss between the experimental and control groups of animals. The results of these experiments do not confirm the view [4, 5] that fibrin films are present on the inner surfaces of the endothelium and basement membranes of the blood vessels, and that these layers play an important role in vascular permeability.

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