MACROPROTEINEMIA AND THE PROGNOSIS IN BLOOD LOSS

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UDC 616-001.5-092.9-07:616.153.96

KEY WORDS: blood plasma macroproteins; blood loss; prognosis.

Problems relating to prognosis often arise in experimental models of blood loss: determination of transformation of blood loss into hemorrhagic shock [7], prevention of irreversible changes [14], and standardization of the initial conditions for the evaluation of the results of treatment [5]. For predicting the outcome of states of this kind, parameters of the hemodynamics [2, 12], the level of anaerobic glycolysis [4], activity of biogenic amines [1], the relationship between the various hematologic parameters [3, 8], and the plasma protein deficit [10] have been studied. The writers showed previously that the plasma macroprotein level can be used as an indicator of reactivity of animals in various extremal states [9].

The aim of this investigation was to assess the prognostic value of macroproteinemia in a model of prolonged blood loss in dogs. From the practical point of view it was important to predict the duration of the phase of blood pressure (BP) compensation, the total number of exsanguinations, and the volume of the blood loss sustained by a particular animal.

EXPERIMENTAL METHOD

A retrospective analysis was made of experiments on 70 mongrel dogs (body weight 7-19 kg; pentobarbital anesthesia, 30 mg/kg). A model of prolonged blood loss [6] was created by repeated (every 15 min) bleedings from the femoral artery until BP was 5.3 kPa. If BP did not rise in the course of 15 min, the interval between exsanguinations was increased to 30, 45, or 60 min. The time from the initial bleeding to spontaneous lowering of BP (4.0-3.3 kPa) was measured with an accuracy of 5-6 min and was taken as an estimate of the duration of the compensation phase of BP (T). The initial (V_0) and total (V_t) volume of blood lost, the hematocrit index (H), the total plasma protein concentration (C), and the concentrations of macroproteins (M) and albumin (A) in samples of plasma taken in the initial state and at the end of the experiment were measured. To determine the protein parameters, techniques described previously [9] were used. The data were subjected to statistical analysis by parametric methods [11].

EXPERIMENTAL RESULTS

According to the majority of parameters of the blood system in the initial state all the dogs investigated can be included in the same population. The exception was the M concentration (in %) in the plasma before the experiment. In 52 animals (sample B1) this parameter varied from 13 to 27%, and corresponded on the whole to the normal level of M, as shown previously [9]. In nine dogs (sample B2) the initial level of M was abnormally high – over 33.8% ($\bar{x} + 3\sigma$) – or was raised – over 29% ($\bar{x} + 2\sigma$). No other deviations from normal were found in animals of the B2 sample. Parameters H and of the blood protein system agreed on the whole with the normal distribution, with typical values of coefficients of asymmetry and excess. The arithmetic means and their errors for samples B1 and B2 are given in Table 1.

The distribution of the animals by number of exsanguinations (i) during time T is characterized as a whole by the sum of mutually geometrically independent distributions of random values, and is satisfactorily described by a Poisson distribution with mean $\bar{x} = 6.014$. The chi-square test confirmed agreement between the empirical and theoretical frequencies with a high degree of significance.

All-Union Hematologic Research Center, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR O. K. Gavrilov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 107, No. 4, pp. 415-417, April, 1989. Original article submitted April 20, 1988.

 0007-4888/89/0004-0462$12.50

TABLE 1. Parameters of Blood System of Dogs before and after Blood Loss and Analysis of Correlation between Them

Before blood loss \ After blood loss		V_0, ml/kg 36.1±1.3 (58) 39.2±4.9 (8)	V_t, ml/kg 52.4±1.6 (57) 54.4±4.7 (8)	i 6.2±0.3 (52) 6.5±0.9 (8)	T, h 1.92±0.08 (60) 2.48±0.23 (9)
H, liters/liter	0,497±0,009 (49) 0,487±0,022 (9)	−0,106 0,334	−0,178 0,003	0,111 −0,780*	0,106 −0,297
C, g/liter	60,7±1,2 (56) 62,0±4,6 (9)	0,033 −0,660	−0,143 −0,662	0,008 0,036	−0,222 −0,373
M, g/liter	12,8±0,4 (50) 19,4±1,8 (9)	0,015 −0,605	−0,090 −0,602	−0,012 −0,112	−0,164 −0,579
M, %	20,6±0,5 (52) 31,4±0,8 (9)	−0,020 −0,306	−0,032 −0,343	0,099 −0,294	−0,328** −0,809**
A, g/liter	23,0±0,5 (50) 17,3±1,4 (9)	0,089 −0,484	−0,016 −0,315	0,097 0,267	−0,278* −0,410
A, %	37,8±0,5 (52) 27,6±1,5 (9)	0,064 −0,178	0,227 0,137	0,241 0,572	−0,065 −0,004

Legend. *$p < 0.05$, **$p < 0.02$. Values of $(\bar{x} \pm m)$ and coefficient of correlation r given in Table 1; number of animals studied shown in parentheses. Numerator – sample B1, denominator – B2.

The frequency distribution of the duration of the compensation phase of BP can be described by the γ-function

$$f(T) = \{\Gamma(a)\}^{-1} \cdot b^a \cdot T^{a-1} \cdot e^{-bT}. \quad (1)$$

Estimates of parameters of distribution (1) were calculated for the total population of experimental dogs (B1 + B2): $a = 7.79$; $b = 3.96$. No differences were found in the distribution of the value of T in the two samples. That the Γ-function is appropriate for the total set of data for T is confirmed by the satisfactory agreement between the empirical and theoretical frequencies ($\chi^2_{12} = 17.82$; $p < 0.05$).

The individual response of the animals to blood loss varied within wide limits; variations of each of the parameters studied were expressed equally. The statistical stability of the parameters, estimated as the range of variation, decreased in the following order: V_t (24-79 ml/kg)–V_0 (13-51 ml/kg)–i (3-13)–T (0.1-4.2 h). This means that the prognostic value of the parameter T is probably higher than that of the other parameters. This type of relationship was confirmed by the results of correlation analysis (Table 1).

During analysis of the set of initial and final values, significant dependence was found between the M_0 concentration (in %) in the dogs' plasma before the experiment and the duration of the compensation phase of BP. This dependence can be described by a linear regression equation separately for samples B1 (2) and B2 (3):

$$T = 13.50 - 0.56M_0, \quad (2)$$

$$T = 11.82 - 0.29M_0. \quad (3)$$

Both equations are significant at the $p = 0.02$ level. With an abnormally high initial level of M, the dependence is characterized by a very strong degree of correlation ($r = -0.809$). Thus an increase in the relative concentration of macromolecular proteins in the plasma corresponds to reduced resistance of the animal to prolonged blood loss and can be regarded as an unfavorable prognostic sign. In such animals decompensation of vascular tone develops earlier and the mechanism maintaining the circulating blood volume acts less effectively.

How is the influence of the blood protein system on the course of prolonged blood loss realized? It is difficult to imagine the selective exhaustion of the reserves of one particular protein or one protein fraction under conditions of blood loss. For example, changes in the M concentration in the course of prolonged blood loss were minor: before the

experiment 22.4 ± 2.4% (n = 42), 1 h later 21.1 ± 0.8% (20), and at the end of the experiment 20.4 ± 2.7% (36). Indirect participation of the protein as a carrier of physiologically active compounds and as one of the important components of the microenvironment of the blood cells, creating optimal conditions of activity for them with respect to physical and chemical parameters, would seem to be a more realistic explanation. Data continue to be published on interprotein relations in the plasma and the different physiological activity of the complexes thus formed [9], and on participation of plasma factors in cell aggregation processes [13]. It can be assumed that even relatively small deviations of the absolute and relative concentrations of proteins in the blood plasma from the optimum will lead – through changes of viscosity, of colloid-osmotic pressure, and of other physicochemical parameters – to intensification of the functional disorders characteristic of blood loss and, in particular, of hypoxia.

Individual prediction of experimental blood loss can best be begun with determination of protein parameters in the initial state and calculation of the value of T by equation (2). If the level of M is abnormally high, equation (3) is used. To predict the number of exsanguinations and the volume of blood lost (correlation between these parameters and the state of the protein system was not demonstrated in this investigation), the Poisson frequency distribution and Γ-function (1) can be used, with precise stochastic estimation of the value of T.

During trials of the proposed scheme in 13 experiments with prolonged blood loss, deviations of the calculated estimates of T from the results of observations averaged ±30%. As a result of this prediction, the wastage of animals due to "overdosage" of the blood loss and the development of a state of irreversibility can be reduced.

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