CORRECTION OF DISTURBANCES OF THE SYSTEM REGULATING THE AGGREGATE STATE OF BLOOD IN THE POSTRESUSCITATION PERIOD BY IONOL

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A fundamental problem in resuscitation is the prevention of post-resuscitation changes in the organs and systems of the revived organisms [10]. Despite advances in the prevention and treatment of postresuscitation complications, mortality from pathology of hemostasis reaches 50-65% [2, 10, 11]. Processes of lipid peroxidation (LPO) are known to be involved in the genesis of many pathological, including terminal, states [1, 3, 10]. This paper describes a study of the possibility of preventing postresuscitation disturbances of the system regulating the aggregate state of the blood by preliminary administration of ionol, an effective scavenger of free radicals [1], with a hypocoagulation and fibrinolytic action [6]. Ionol is quickly absorbed and distributed in the organs and tissues, it is metabolized slowly, and eliminated from the body relatively slowly [1].

EXPERIMENTAL METHOD

Experiments were carried out on 248 noninbred albino rats weighing 180-210 g, anesthetized with pentobarbital (25 mg/kg); 43 animals constituted the control group (I). The 112 rats of group II were subjected to acute mechanical asphyxia, leading to clinical death. The 24 intact rats of group III received ionol, and the 105 rats of group IV were treated with ionol before clinical death. Clinical death was induced by clamping the intubation tube for 7 min, and the animals were resuscitated by artificial ventilation of the lungs combined with indirect cardiac massage. Ionol was injected intraperitoneally in a dose of 100 mg/kg 48, 24, and 1 h before asphyxia (the time required to absorb the preparation and to ensure its uniform distribution in the blood and internal organs). Blood for investigation was taken from the heart at the end of asphyxia, and during the resuscitation period, 90 min, 3 and 6 h, and 1 and 3 days after asphyxia. Blood with the addition of sodium citrate (9:1) was centrifuged at 3200 g in order to obtain plasma. The coagulating properties of the blood were assessed relative to the following parameters: the end of clotting time (T_2), calculated from the shape of the electrocoagulogram, recorded on the N-334 instrument, the number of circulating platelets, the prothrombin and thrombin time, the fibrinogen concentration, fibrinogen B, and fibrinolytic activity [5].

EXPERIMENTAL RESULTS

Prophylactic administration of ionol before acute mechanical asphyxia considerably increased the survival rate of the rats after resuscitation (84.7% compared with 59.2% of resuscitated animals without the use of ionol) and reduced mortality in the early postresuscitation period more than threefold. Ionol led to the earlier appearance of cardiac contractions after the beginning of resuscitation and to restoration of spontaneous respiration, the appearance of a corneal reflex, and of spontaneous movements.

Mechanical asphyxia caused phasic changes in blood clotting and fibrinolysis, manifested as reactive hypercoagulation, which appeared at the end of clinical death and continued until the 90th minute of the resuscitation period, with transition after 3 h into phase 1 of the disseminated intravascular blood clotting (DIVC) syndrome – the hypercoagulation phase.

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TABLE 1. Time Course of Changes in Parameters of System Controlling Aggregation State of the Blood in Albino Rats after Asphyxia (M ± m)

Parameter	Experimental conditions							
	control (I)	asphyxia (II)	time after beginning of resuscitation (II)					
			5 min	90 min	3 h	6 h	1 day	3 days
T_2, sec	254,1±7,81	174,4±8,21***	209,6±12,2***	206,7±9,12**	185,3±7,97***	339,2±23,4**	226,0±10,3*	197,3±4,23***
Platelet count, $\times 10^9$/liter	357,5±15,8	142,6±8,84***	149,6±11,7***	326,7±13,5	314,6±9,66	145,6±3,03***	159,7±6,50***	356,1±16,7
Prothrombin time, sec	23,1±0,41	18,1±0,23***	27,1±0,53***	17,0±0,35***	20,3±0,35***	36,0±0,63***	34,0±0,54***	19,3±0,40***
Thrombin time, sec	20,2±0,42	17,0±0,25***	24,0±0,39***	18,1±0,41***	21,5±0,54**	32,7±0,99***	29,1±0,50***	18,3±0,48***
Fibrinogen, g/liter	1,83±0,084	1,63±0,064*	1,60±0,081**	1,94±0,082*	1,67±0,019*	1,32±0,037***	2,21±0,10***	2,63±0,31***
Fibrinolytic activity, min	111,6±4,97	68,7±2,82***	69,4±2,77***	172,5±19,1**	232,7±7,82***	158,5±7,32*	89,6±6,13*	79,7±6,17***
Fibrinogen B, points	—	+ —	+ + +	+ + +	+ +	+ + +	+ + +	+

Legend. Here and in Table 2, asterisks indicate statistically significant differences between groups I-II, I-III, and II-IV: *p < 0.1, **p < 0.01, ***p < 0.001.

TABLE 2. Effect of Ionol on Parameters of System Regulating Aggregate State of the Blood in Albino Rats after Resuscitation from Asphyxia (M ± m)

Parameter	Experimental conditions		Time after beginning of resuscitation (IV)					
	control + ionol (III)	asphyxia + ionol	5 min	90 min	3 h	6 h	1 day	3 days
T_2, sec	348,0±1,06***	253,3±14,6***	275,1±16,4**	284,7±7,77***	294,3±10,9***	254,0±6,33***	298,4±9,14***	253,8±5,29***
Platelet count, $\times 10^9$/liter	358,0±3,90	277,8±10,9***	285,7±7,65***	345,8±10,7	339,1±6,62*	294,2±9,03***	347,3±14,7***	360,2±2,83
Prothrombin time, sec	36,0±1,72***	22,0±0,54***	24,1±0,50***	26,4±0,75***	27,3±0,56***	26,0±0,18***	28,2±0,39***	24,3±0,46***
Thrombin time, sec	24,0±0,14***	20,2±0,66***	23,3±0,17***	22,3±0,62***	23,5±0,37***	21,1±0,26***	24,1±0,50***	20,2±0,33***
Fibrinogen, g/liter	2,32±0,14***	2,11±0,064***	2,02±0,078***	2,31±0,093**	2,60±0,068***	2,44±0,082***	2,85±0,071***	2,53±0,10
Fibrinolytic activity, min	224,0±14,8***	110,0±11,3**	96,5±5,49***	107,5±3,24**	122,7±3,16***	137,2±3,56*	110,5±7,48*	110,8±4,0**
Fibrinogen B, points	—	—	+	+	+ —	—	+ —	—

After 6-24 h the second phase of DIVC syndrome (hypocoagulation) was observed, with the development of coagulopathy affecting consumption of the blood clotting factors, with subsequent transition after 3 days into a phase of residual manifestations of thrombosis and blockade.

In the animals of group IV (Table 2) administration of ionol prevented the development of the DIVC syndrome and the consumption of blood clotting factors, reduced fibrinolytic activity, and under conditions of pharmacologic protection, it established the hemostatic potential at a new level [11], thereby improving the microcirculation by a certain degree, preventing the formation of "shock" organs, and reduced the postresuscitation mortality (from 68.4 to 21.6% in the experiments).

It has been shown in recent years that in addition to toxemia, excess of catecholamines, metabolic acidosis, etc., an essential role in the pathogenesis of postresuscitation sickness is played by excessive activation of LPO processes, induced by hypoxia, ischemia, and subsequent resuscitation with reoxygenation and recirculation [9]. Correlation has been demonstrated between activation of LPO processes and activation of blood clotting [7]. Ionol, inhibiting LPO in biological membranes and in organs and peripheral formations of the system controlling the aggregate state of the blood, reduces activity of lipases and phospholipases, which bring about hydrolysis of cell membrane phospholipids [3]. One result of this may be a decrease in the content of phospholipids which participate in thromboplastin formation, namely phosphatidylethanolamine, phosphatidylserine, lysophosphatidylcholine, and cardiolipin [4]. Thromboplastin is the immediate cause of development of thrombohemorrhagic changes [2, 8], and the kinetics of its formation affects the whole subsequent cascade of coagulation hemostasis [12]. Analysis of data in the literature and of the results of our own investigations leads to the suggestion that ionol, weakening the disturbance of arachidonic acid metabolism, can potentiate the synthesis of prostacycline which, in turn, leads regularly to changes in the platelet-vascular component of hemostasis [11].

The results of these investigations thus indicate that prophylactic administration of ionol is a highly effective means of preventing post-resuscitation disturbances of the system controlling the aggregate state of the blood in terminal states.

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