https://doi.org/10.23873/2074-0506-2022-14-3-301-311

The place of glucosylated enteral solution in the correction of hemorheological abnormalities in acute poisoning by psychopharmacological drugs

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Abstract

Introduction. *In acute exogenous poisoning, hemorheological abnormalities are observed. Various extracorporeal, physico-chemical methods are used to correct them. There is an opinion that the enteral route of administration of corrective agents may be a more physiological way to restore homeostatic imbalances.*

Aim. *To conduct a comparative assessment of the effect of glucosylated enteral solution and standard infusion therapy on hemorheological abnormalities in acute poisoning by psychopharmacological drugs.*

Material and methods. *Patients with acute poisoning by psychopharmacological drugs who were treated at the N.V. Sklifosovsky Research Institute for Emergency Medicine in 2017-2021 were examined. Of these, 23 people, in whose treatment the enteral correction program was used, made up the study group, and 22 patients (the comparison group) underwent a standard set of therapeutic measures.*

Indicators of hemorheological status were examined on the 1st, 3rd and 5th days of ongoing therapy. Statistical data analysis was carried out using the Statistica 10 software package (StatSoft, Inc., USA).

Results. *The use of a glucosylated enteral solution led to a reduction in plasma viscosity under normal hematocrit conditions at all follow-up periods. In patients of both groups, there was a decrease in blood viscoelasticity under conditions of high shear potential at all stages of the study, which indicated an impaired red blood cell deformability. This process was more pronounced in individuals of the comparison group. The conducted studies have shown that the use of infusion therapy and glucosylated enteral solution in the early stages of acute poisoning by psychopharmacological drugs generally has a unidirectional positive effect on hemorheological indicators contributing to the stabilization of blood circulation. At the same time, the effect of glucosylated enteral solution therapy is faster and more pronounced.*

Conclusions. *The use of glucosylated enteral solution and infusion therapy as a supportive treatment in the early period of acute poisoning by psychopharmacological drugs in most cases has a unidirectional effect on hemorheological parameters. In cases of glucosylated enteral solution therapy, there was an outrunning positive dynamics on the part of the majority of the studied hemorheological parameters. Glucosylated enteral solution can be the method of choice as a maintenance therapy*

after the end of detoxification process for acute poisoning by psychopharmacological drugs.

Keywords: acute poisoning, psychopharmacological drugs, enteral correction program, glucosylated enteral solution, hemorheology

Conflict of interests Authors declare no conflict of interest

Financing The study was performed without external funding

For citation: Potskhveriya MM, Ilyashenko KK, Belova MV, Simonova AYu, Bitkova EE. The place of glucosylated enteral solution in the correction of hemorheological abnormalities in acute poisoning by psychopharmacological drugs. *Transplantologiya. The Russian Journal of Transplantation.* 2022;14(3):301–311. (In Russ.). https://doi.org/10.23873/2074-0506-2022-14-3-301-311

GES - glucosylated enteral solution

IL - intestinal lavage

EAIm - erythrocyte aggregation index at rest

$EAIm_1$ - erythrocyte aggregation index in flow at a shear rate of 3 s^{-1}

PPPA - poisoning with psychopharmacological agents

ECP - enteral correction program

SES - saline enteral solution

Introduction

It has now been proven that various nosological types of acute exogenous poisoning are accompanied by typical homeostasis disorders. Their severity is directly dependent on the poisoning severity and stage, and also determines the prognosis of the disease, the volume and intensity of therapeutic measures [1–3].

Among these disorders, hemorheological profile disorders play an important role. It has been proven that Most exotoxicoses, including poisoning with psychopharmacological agents (PPPA), have been proven be accompanied by the development of hyperviscosity syndrome with a

significant increase in hematocrit, aggregation activity of erythrocytes and platelets, plasma and blood viscosity [4, 5].

Previous clinical experience has shown that highly effective methods of artificial blood detoxification used in the complex of therapeutic measures, blood exposure to physical (laser and ultraviolet irradiation) and chemical (sodium hypochlorite, ozone) factors often have a corrective effect on impaired homeostasis parameters and significantly influence the course of the pathological process and the outcome [1, 6, 7].

So, as a result of hemosorption, predominant changes characterized by a decrease or normalization of the increased baseline aggregation of blood cells, were found in hemorheological parameters. Additional correction of the hemorheological status is greatly facilitated by magnetic hemotherapy, which is used before the onset of hemosorption [6]. In the rehabilitation period of acute poisoning, hemorheological disorders are coped with by means of intravenous laser hemotherapy, as well as the EHF-therapy, which has a modulating effect manifested by a shift of hemorheological parameters towards the norm, after their baseline multidirectional deviation from normal at baseline [4, 8].

There has been evidence of a positive effect of the hyperbaric oxygenation on the hemorheological profile [9]. I.A. Burykina et al. [10] have found a positive effect of intestinal lavage (IL) on elevated baseline hemorheology parameters, which was characterized by reductions in apparent blood viscosity at high and low shear rates, plasma viscosity, and erythrocyte aggregation.

It should be noted that at present, the infusion-transfusion therapy remains a widely used method for the correction of homeostasis disorders, despite its existing shortcomings [1, 11]. At the same time, there is an opinion that a more physiological way to restore homeostasis disorders

may be the administration of corrective agents by the enteral route [12-14].

The aim of the study was to conduct a comparative assessment of the effect of glucosylated enteral solution and standard infusion therapy for hemorheological disorders in acute poisoning with psychopharmacological drugs.

Material and methods

Conducted An open-label randomized prospective study was conducted on the base of the Department of Acute Poisoning and Somatopsychiatric Disorders of the N.V. Sklifosovsky Research Institute for Emergency Medicine in the period from 2019–2021. The study was approved by the Biomedical Ethics Committee (excerpt from Protocol No. 5-16 dated November 21, 2016). The patients were enrolled in accordance with the inclusion criteria: PPPA, patient age under 65 years old, severe intoxication state (coma). The intoxication severity was assessed taking into account the baseline level of consciousness impairment according to the Classification by E.A. Luzhnikov [1]. The exclusion criteria were: age under 18 years, PPPA of mild or moderate severity.

Forty five patients (27 women and 18 men) were followed up, 23 of whom were treated according the enteral correction program (ECP) and constituted the study group; and 22 patients were given a standard set of therapeutic measures (comparison group). The patient allocation into groups was random, patients of both groups were comparable in gender, age, and PPPA severity.

ECP included two stages. At the first stage, patients of the study group, upon admission to the hospital for the purpose of detoxification, underwent IL using saline enteral solution (SES) [1].

After the end of IL, the second stage of ECP was started: fractional oral administration of glucosylated enteral solution (GES), which is an SES supplemented with 2 g of glucose per liter took place in the next 4 days. It was administered in doses of 200 ml at regular intervals in a total volume of 3–4 liters per day. Hylak forte was added into GES, 60 drops 3 times a day, and Pektovit was also prescribed 5.5 g 3 times a day. In this case, infusion therapy was excluded.

In the comparison group, the treatment was also provided in two stages. At the first stage, extracorporeal methods, forced diuresis, and intravenous infusions were used as the detoxification therapy. At detoxification completion, at the second stage, a maintenance infusion therapy was performed in a volume of 2–3 liters per day for the following 4 days.

In this article, we do not consider the effect of the detoxification methods used (treatment stage 1) on hemorheology parameters, since the results of these studies were published earlier [14].

Comparison was made between groups at the second stage of treatment, when on the 1st, 3rd and 5th days an ongoing therapy course (GES in the study group and infusion therapy in the comparison group), hemorheological profile was studied. The study of blood viscosity and viscoelasticity was performed on a capillary viscometer BioProfiler (USA). The analysis of the results included the evaluation of the parameters corresponding to the rheological model: the leading factor determining blood viscosity is the deformability of erythrocytes at a high shear rate of 62.8 s^{-1}; and the erythrocytes aggregation at a low shear rate (2.5 $s^{-}1$),; at a mean shear rate of 12.6 s^{-1}, the formation of clusters resembling a stack of coins of erythrocytes starts [15]. Erythrocyte aggregation index at rest (EAIm) and that in flow at a shear rate of 3 s^{-1}

($EAIm_1$) were determined on an aggregometer MA-1 (Myrenne GmbH , Germany) [16]. Platelet aggregation in whole blood was determined using an impedance CHRONO-LOG aggregometer (USA). The aggregation inducer was collagen at the concentration of 2 mg/mL created in tested blood. Platelet aggregation activity was assessed by the maximum amplitude of the aggregation curve and expressed in Ohms [17]. Hematocrit was measured on an Act diff 2 Beckman Coulter Hematology Analyzer (USA). Parameters obtained at investigation of 45 blood donors (30 men and 15 women) aged 20–40 years were used as normal values.

The statistical analysis of data was performed using the Statistica 10 Software Package (StatSoft, Inc., USA). The normality of data distribution was assessed using the Shapiro–Wilk test ($n \leq 50$). Due to the fact that the distribution differed from the normal one, non-parametric statistical methods were used. The results were presented as median (Me), 25th and 75th percentiles of Me (Q25–Q75). Comparison of quantitative data between groups was made using the Mann-Whitney test (independent groups) and Wilcoxon test (linked groups). $P<0.05$ was taken as the level of statistical significance.

Study results

The results obtained are shown in the Table. Investigations conducted one day after the start of treatment showed normal baseline hematocrit values in patients of both groups. A 1.3-time decrease in plasma viscosity was found in the study group compared to normal. Patients of both groups had similar values of EAIm that were lower than normal by a mean of 1.25 times. Meanwhile, $EAIm_1$ showed a tendency to increase. Platelet aggregation had different trends: it was increased by 1.3 times in patients of the study group, and it approached the reference values in the comparison group. The platelet count exceeded the norm by

1.4 times in the study group, and it was within the reference range in the comparison group.

Blood viscosity at all shear rates in the study group showed a downward trend, and in patients of the comparison group it was statistically significantly reduced by 1.7 to 1.3 times. A similar situation in general was also noted in terms of blood viscoelasticity.

Table. Comparative assessment of the effect of glucosylated enteral solution and standard infusion therapy on hemorheological abnormalities in acute poisoning by psychopharmacological drugs

Parameters	Norm	Study stages					
		1st day		3rd day		5th day	
		Study group	Comparison group	Study group	Comparison group	Study group	Comparison group
Hematocrit, %	40.4 (40.05;40.76)	39.0 (37.7;42.7)	38.8 (32.5;41.2)	40.70 (37.30; 42.70)	41.0 (35.0;43.0)	40.00 (35.90;43.80)	42.2 (29.2;44.5)
Plasma viscosity, mPa×s	1.80 (1.78;1.82)	1.32* (1.26;1.37)	1.95 (1.8;2.1)	1.37* (1.29;1.57)	2.35 *;1 (1.8;2.5)	1.36* (1.27;1.49)	2.3* (1.67;2.62)
Resting erythrocyte aggregation index	15.6 (15.02; 16.18)	12.60 (10.3;14.6)	12.09 (11.8;18.54)	15.40 (14.30;16.40)	14.73 (13.1;20.45)	15.70 (14.70;19.50)	17.5 (12.9;19.3)
Index of erythrocyte aggregation in flow	18.19 (18.17;19.63)	21.80 (21.1;30.3)	20.4 (19.7;28.6)	26.60 (23.80; 29.80)	28.02*;1 (26.0;33.3)	28.00 (26.10;34.00)	30.5 *;1 (27.3;33.5)
Platelet aggregation, Ohm	13.0 (12.6;13.6)	17.0* (14.0;19.0)	14.0* (5.3;17.3)	20.0* (15.0;22.0)	19.0* ;1 (16.5;18.9)	17.0* (16.0;20.0)	17.2* (14.2;18.3)
Platelet count, 10^9/L	196 (187.6;204.4)	274.0 (213;322)	194.0 (126;242)	217.0 (166.0;235.0)	186 (129;199)	222.0 (186.0;275.0)	221 (134.5;275.5)

Table continued

Parameters		Norm	Study stages					
			1st day		3rd day		5th day	
			Study group	Group comparisons	Study group	Comparison group	Study group	Comparison group
Blood viscosity, mPa×s at shear rate	2.5 s^{-1}	5.9 (5.75;6.05)	5.10 (4.66;5.71)	3.39* (2.67;5.76)	5.49 (4.90;6.28)	4.03 (3.55;5.55)	5.21 (4.58;5.83)	4.0 (3.56;6.5)
	12.6 s^{-1}	4.8 (4.68;4.92)	4.04 (3.86;5.32)	3.01* (2.54;5.2)	4.60 (3.83;4.96)	3.14* (2.67;4.46)	4.53 (3.92;5.96)	3.83 (3.44;5.4)
	62.8 s^{-1}	4.1 (4.02;4.15)	3.72 (3.33;5.25)	3.1* (2.28;4.68)	4.19 (3.64;5.13)	3.69 (3.2;4.01)	4.28 (4.21;5.16)	3.63 (3.06;4.53)
Visco-elasticity, mPa×s, at shear rate	2.5 s^{-1}	3.13 (3.02;3.24)	2.80 (2.50; 3.97)	1.67* (1.22;2.92)	2.73 (2.63;3.16)	2.01* (1.74;3.07)	2.96 (2.51;4.51)	1.99* (1.73;4.24)
	12.6 s^{-1}	1.55 (1.48;1.62)	1.49 (1.30;2.61)	0.74* (0.05;1.95)	1.35 (1.33;1.83)	1.01* (0.64;1.29)	1.89 (1.52;2.85)	0.86* (0.69;2.04)
	62.8 s^{-1}	0.61 (0.57;0.65)	0.31* (0.26;0.55)	0.60 (0.28;0.63)	0.29* (0.24;0.33)	0.58 (0.19;0.70)	0.30* (0.19;0.54)	0.48 (0.21;0.87)
MCV	-	80-100	91.0 (84.9;93.5)	91.8 (88.1;96.1)	90.8 (87.1;94.0)	94.3 (90.1;96.1)	89.5 (84.9;92.9)	91.15 (83.8;93.4)

Notes: * - statistically significant difference from the norm ($p<0.05$, the Mann-Whitney test), [1] - statistically significant difference from the baseline value ($p<0.05$, the Wilcoxon signed rank test), [2] - statistically significant difference from the parameter of the comparison group ($p<0.05$, the Mann-Whitney test)

On the 3rd and 5th days within the treatment course, normal hematocrit values remained in both groups Plasma viscosity did not statistically significantly differ from the previous value in patients of the study group, and in the comparison group on the 3rd day, its increase was noted, exceeding the norm by 1.3 times ($p \leq 0.05$). The achieved values were maintained at the next stage of the study.

EAIm in the study group reached normal values in the following 2 days, while in the comparison group, it was 10% higher than normal on the 5th day ($p > 0.05$). $EAIm_1$ in both groups of patients continued increasing in subsequent stages of treatment to a greater extent in patients of the comparison group. Platelet aggregation at subsequent stages of the study was increased approximately in the same range in patients of the compared groups. The number of platelets varied within the reference range of values.

Slightly reduced baseline blood viscosity in patients of the study group reached normal values on subsequent days at all shear potential rates. In the comparison group, it showed a tendency to normalization, but was lower than in the study group. In the study group, on the 3rd and 5th days, viscoelasticity at a low shear potential rate was within normal range against the background of the administered GES, and it decreased in medium shear rates by 13% from normal on the 3rd day; on the 5th day it exceeded the normal value by 18%. At a high shear rate, it was no more than 50% of normal at all stages of the study.

In the comparison group, at high and medium shear rates, blood viscoelasticity was statistically significantly reduced at all stages of the study, although it showed a tendency to increase, while at high shear rates it was within the normal range.

The described above demonstrated that using infusion therapy and GES at early stages of PPPA, as a whole, has a unidirectional positive

effect on hemorheology parameters. Meantime, the effect of using GES is faster and more pronounced.

Discussion

The microcirculation system plays an essential role in ensuring adequate blood supply to the body organs and tissues. At this level, both the functions of the intravascular homeostasis system, the endothelium of microvessels, blood cells, and also the rheological properties of blood are very important. The deformation properties of erythrocytes contribute to their optimal distribution over the network of microvessels; and the ability of erythrocytes to reversible aggregation determines the blood rheological properties and blood flow characteristics at low flow rates in capillaries. Under natural conditions, and especially in pathology, the deformation properties of erythrocytes, as well as their ability to aggregate, can change greatly. Blood viscosity in normal and most pathological cases is mainly determined by the erythrocyte volume concentration and erythrocyte ability to aggregation and deformation, which significance is especially essential at the microvascular level [18–20].

For effective tissue perfusion and adequate oxygenation, the mechanisms providing certain parameters of microcirculation, blood rheological profile, and its oxygen capacity should be coordinated [20, 21]. Previously, it was shown that plasma viscosity, hematocrit, and erythrocyte deformability act as factors regulating the functional capillary density and arteriole tone [22].

We found that in patients of both groups, hematocrit values at all stages of the study were generally within normal range. In patients of the study group, the blood plasma viscosity decreased with the course of GES intake, while in the comparison group, it remained elevated. This is

probably due to different concentrations of plasma proteins, especially fibrinogen and immunoglobulins, in patients of the study group. A number of studies have shown that a decrease in plasma viscosity leads to a decrease in shear stress on the capillary wall, a decrease in the nitric oxide production by vascular endothelial cells, which negatively affects microcirculation. On the other hand, a moderate increase in hematocrit may contribute to the increase in the density of functioning capillaries [21, 23, 24].

In patients of the study group, despite reduced plasma viscosity, the blood viscosity did not statistically significantly differ from normal at all stages of the study; and in the comparison group, on the contrary, the reduced blood viscosity coincided with increased plasma viscosity.

Among the factors affecting blood viscosity, the erythrocyte deformability has been noted, which is closely related to the viscoelasticity of blood. In patients of the study group, viscoelasticity showed a tendency to decrease at low and medium shear rates at all stages of the study, and in the comparison group, its statistically significant decrease was revealed. Meantime, at a high shear rate, an opposite situation took place.

The most significant reason for changes in erythrocyte deformability is oxidative stress-induced changes in the protein and lipid structures of cell membranes [3, 21].

It is known that oxidative stress develops with various toxicants, including psychotropic drugs, entering the body and leads to damage to the erythrocyte membrane lipid layer [25]. These derangements result in a decreased deformability of erythrocytes and blood flow disorders at the microcirculation level, which in our studies has been confirmed by a significant decrease in viscoelasticity at a high shear potential rate.

The erythrocyte deformability impairments, in turn, are accompanied by their aggregation disorders. This has been indicated by the increased values of the erythrocyte aggregation index in flow that we have revealed.

It is known that erythrocyte aggregation significantly affects blood viscosity at relatively low shear rates [26, 27]. Therefore, when blood flow slows down, one can assume an increment in erythrocyte aggregation and an increase of its contribution to the viscosity resistance to blood flow [20]. Meanwhile, the aggregation can have a positive effect on the blood flow, for example, by participating in the sigma-effect formation and hematocrit decrease in microvessels [28, 29].

The revealed changes in the hemorheological profile at an early stage of acute PPPA, which occur when using GES and a standard infusion therapy in the treatment complex, reflect the nature of the functional systems that are formed at the treatment stages in order to create an adaptive effect to maintain microcirculation at a level corresponding to requirements of this pathological situation [30].

At that, GES has a more pronounced positive effect in hemorheological disorders in this group of patients.

Conclusions

1. The use of glucosylated enteral solution and infusion therapy as a maintenance treatment in the early period of acute poisoning with psychopharmacological agents has a unidirectional effect on the parameters of the hemorheological profile in most cases.

2. When using glucosylated enteral solution, advanced positive dynamics is determined in the majority of the studied hemorheological parameters.

3. The use of glucosylated enteral solution may be the method of choice as a maintenance therapy after completing the detoxification measures for acute poisoning with psychopharmacological agents.

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The article was received on March 11, 2022;
approved after reviewing April 4, 2022;
accepted for publication June 29, 2022