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# INFLUENCE OF DIFFERENT QUALITATIVE COMPOSITION OF INFUSION SOLUTIONS ON CEREBRAL HEMODYNAMICS IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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## ABSTRACT

**The aim:** Investigate the effect of 0.9% NaCl, HES 130, HAES-LX-5% and mannitol 15% on cerebral hemodynamics in patients with AIS.

**Materials and methods:** The study included 100 patients with AIS. As the investigated solutions were used: isosmolar 0.9% NaCl, hyperosmolar mannitol 15%, colloid-isoosmolar HES 130, colloid-hyperosmolar HAES-LX-5%. The control group received only 0.9% NaCl compared: 0.9% NaCl+HES 130, 0.9% NaCl+HAES-LX-5%, 0.9% NaCl+mannitol 15%. Evaluation of cerebral hemodynamic (indexes of cerebral blood flow) was performed using doppler ultrasound of cerebral arteries.

**Results:** The dynamics of specific volume velocity of blood flow per 100 grams of brain substance indicates that in the group of 0.9% NaCl and 0.9% NaCl+mannitol is the tendency to decrease the blood flow of the brain during 7 days of treatment, respectively: 2.8% and 7.5%. In patients with HES 130 solution cerebral blood flow increases by 14.2%, whereas when applied HAES-LX-5% during 7 days, it increases by 43.2% (p=0.004).

**Conclusions:** The analysis of the data of treatment the patients with AIS showed the best effect (p=0.004) of improvement of the cerebral circulation in the use of the polyfunctional infusion solution HAES-LX-5% unlike the 0.9% NaCl group and group of 0.9% NaCl+mannitol where was a decrease of the dynamics of cerebral blood flow, which could lead to hypoperfusion of the brain.

**KEY WORDS:** acute ischemic stroke, infusion therapy, 0.9% NaCl, HES 130, mannitol, HAES-LX-5%

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## INTRODUCTION

Despite the dynamic development of medicine, mortality from acute ischemic stroke (AIS) remains one of the leading causes of death worldwide. [1, 2]. Dehydration is often observed in patients with AIS, which causes a number of disturbances in the body's homeostasis (reduces cerebral perfusion, increases blood viscosity, etc.) potentially increasing the degree of hypoxia in the penumbra. Many studies today argue that the treatment of AIS should avoid both dehydration and hypervolemia [3, 4]. Today it is known that it is necessary to restore the level of normovolemia as early as possible, which contributes to the restoration of collateral perfusion and, in the future, can reduce the mortality and disability of patients with AIS. At present, there are no clear recommendations for the infusion therapy algorithm in the treatment of AIS [3, 4, 5].

Taking into account the above-mentioned little-to-one, the question remains the influence of infusion solutions of different qualitative composition on the state of cerebral hemodynamics in patients with acute cerebral ischemia.

## THE AIM

Investigate the effect of 0.9% NaCl, HES 130, HAES-LX-5% and mannitol 15% on cerebral hemodynamics in patients with AIS.

## MATERIALS AND METHODS

The study included 100 patients with AIS (non-differentiated by pathogenetic subtype). Randomization was performed using random numbers. The average age of patients was 71.84 ± 1.67 years, of which 47 were men and 53 women. The study included patients whose body weight did not exceed 120 kg. The study groups did not differ in age composition, severity of disease and other outcomes that could affect the final results of the study.

Diagnosis of AIS was established on the basis of computer tomography data. The main criterion for the selection of patients was the presence of AIS in patients and disturbances of consciousness on a scale of Glasgow 12 points and below, but not less than 4 points at admission (average was 12 points). Investigated solutions:

An isosmolar 0.9% NaCl solution in 1 ml as a crystalloid base contains sodium chloride 0.009 g, theoretical osmolarity – 308 mosmol/l.

The colloid-isosmolar solution hydroxyethylcrystal 6% 130/04 (HES 130) contains 1000 ml of colloidal base (O-2-hydroxyethyl) starch (molar substitution degree – 0.4; average molecular weight – 130000 Da) 60.0 g, sodium chloride 9.0 g, auxiliary substances: sodium hydroxide (for pH correction), hydrochloric acid (for pH adjustment), water

**Table I.** Dopplerography of extracranial cerebral arteries under the influence of treatment of AIS 0.9% NaCl

| Indexes | Examination | | p |
|---|---|---|---|
| | №1 | №2 | |
| | NaCl 0,9% | | |
| CCA right Vp | 73 (53; 74) | 75 (56; 76) | 0,69 |
| CCA left Vp | 70 (35; 71) | 66 (38; 71) | 0,84 |
| ICA right Vp | 72 (67; 77) | 75 (64; 77) | 0,88 |
| ICA left Vp | 62 (61; 77) | 70 (60; 78) | 1,00 |
| ECA right Vp | 67 (58; 111) | 68 (62; 110) | 1,00 |
| ECA left Vp | 95 (90; 100) | 94 (85; 116) | 0,84 |
| VA right Vp | 49 (44; 50) | 37 (35; 43) | 0,04 |
| VA left Vp | 42 (32; 51) | 45 (32; 50) | 0,88 |
| CCA right IP | 0,64 (0,62; 0,72) | 0,66 (0,65; 0,76) | 0,54 |
| CCA left IP | 0,71 (0,69; 0,81) | 0,70 (0,67; 0,70) | 0,69 |
| ICA right IP | 0,52 (0,45; 0,64) | 0,59 (0,44; 0,70) | 0,88 |
| ICA left IP | 0,53 (0,52; 0,63) | 0,55 (0,48; 0,65) | 1,00 |
| ECA right IP | 0,78 (0,70; 0,79) | 0,73 (0,68; 0,83) | 0,91 |
| ECA left IP | 0,78 (0,77; 0,84) | 0,73 (0,72; 0,78) | 0,42 |
| VA right IP | 0,63 (0,54; 0,70) | 0,74 (0,61; 0,86) | 0,03 |
| VA left IP | 0,66 (0,58; 0,71) | 0,63 (0,61; 0,66) | 0,88 |
| CCA right Pi | 1,20 (1,10; 1,37) | 1,25 (1,25; 1,43) | 0,69 |
| CCA left Pi | 1,33 (1,23; 1,87) | 1,25 (1,12; 1,36) | 0,54 |
| ICA right Pi | 0,90 (0,74; 1,22) | 0,90 (0,74; 1,22) | 1,00 |
| ICA left Pi | 0,93 (0,85; 1,00) | 0,96 (0,84; 1,20) | 0,84 |
| ECA right Pi | 1,50 (1,28; 1,75) | 1,34 (1,25; 1,76) | 1,00 |
| ECA left Pi | 1,80 (1,60; 3,10) | 2,21 (1,72; 2,70) | 1,00 |
| VA right Pi | 1,08 (0,86; 1,54) | 1,14 (0,85; 1,62) | 0,88 |
| VA left Pi | 1,32 (0,89; 1,70) | 1,17 (0,94; 1,45) | 0,88 |

for injection – up to 1000 ml, electrolytes: $Na^+$-154 mmol/l; $Cl^-$-154 mmol/l, theoretical osmolarity – 308 mosmol/l.

The colloid-hyperosmolar HAES-LX-5% solution (registered in Ukraine in 2013 under the name «Gekoton»), which contains as a colloidal basis poly (0-2-hydroxyethyl) starch (average molecular weight of 130,000 Daltons, the degree of molecular substitution 0.4) – 5%, as well as polyether alcohol xylitol – 5%, sodium lactate – 1,5%, sodium chloride – 0,8%, potassium chloride – 0,03%, calcium chloride – 0,02%, magnesium chloride – 0.01%. The ionic composition of the drug: $Na^+$-270.7 mmol/l, $K^+$-4.0 mmol/l, $Ca^{++}$-1.8 mmol/l, $Mg^{++}$-1.1 mmol/l, $Cl^-$-146.6 mmol/l, CH3CH (OH) $COO^-$-133.8 mmol/l. Theoretical osmolarity – 890 mosmol/l.

A hyperosmolar solution of mannitol 15% (mannitol) – hyperosmolyar crystalloid solution 1000 ml contains of mannitol solution 150 g, auxiliary substances: sodium chloride – 9 g, water for injections to 1 liter, theoretical osmolarity – 1131 mosmol/l.

Patients with AIS were divided into 4 groups: group of 0.9% NaCl (25 patients): patients receiving 0.9% of NaCl in addition to baseline therapy for 7 days; group of HES 130 (25 patients): patients who received 0.9% NaCl+HES 130 in addition to baseline therapy for 7 days; group of HAES-LX-5% (25 patients): patients who received 0.9% NaCl+HAES-LX-5% in addition to baseline therapy for 7 days; group of mannitol (25 patients): patients who received 0.9% NaCl+mannitol in addition to baseline therapy for 7 days.

Infusion solutions were injected intravenously (i/v) at a dose of 2.5 ml/kg at a frequency of 2 times a day; infusion was started immediately upon confirmation of the diagnosis, and then every other day every 12 hours during 7 days. The control group patients received only 0.9% NaCl from infusion solutions were taken, the comparison groups patients received: 0.9% NaCl+HES 130 or 0.9% NaCl+HAES-LX-5% or 0.9% NaCl+mannitol. The comparison groups received not only the test solution at a fixed dose, but also a 0.9% solution NaCl, as, in general, to refuse this solution is impossible. The amount of 0.9% NaCl and the daily volume of infusion (i/v) in each study group did not differ significantly. The total volume of intravenous infusion per day amounted to an average of 1000 [800; 1300]. Basic therapy was determined according to the Order of the Ministry of Health of Ukraine dated 03.08.2012 № 602.

**Table II.** Dopplerography of extracranial cerebral arteries under the influence of treatment of AIS by mannitol

| Indexes | Examination | | p |
|---|---|---|---|
| | №1 | №2 | |
| | MANNITOL | | |
| CCA right Vp | 58 (57; 70) | 70 (68; 76) | 0,69 |
| CCA left Vp | 55 (45; 61) | 58 (51; 64) | 0,58 |
| ICA right Vp | 58 (54; 68) | 46 (40; 58) | 0,02 |
| ICA left Vp | 35 (34; 42) | 47 (44; 50) | 0,30 |
| ECA right Vp | 71 (69; 83) | 84 (68; 98) | 0,73 |
| ECA left Vp | 67 (55; 73) | 58 (52; 75) | 0,93 |
| VA right Vp | 46 (39; 47) | 46 (38; 57) | 0,90 |
| VA left Vp | 43 (36; 47) | 42 (38; 52) | 0,53 |
| CCA right IP | 0,76 (0,74; 0,80) | 0,69 (0,60; 0,70) | 0,15 |
| CCA left IP | 0,73 (0,69; 0,76) | 0,69 (0,62; 0,77) | 0,48 |
| ICA right IP | 0,65 (0,45; 0,69) | 0,59 (0,57; 0,66) | 1,00 |
| ICA left IP | 0,58 (0,57; 0,62) | 0,59 (0,58; 0,65) | 0,54 |
| ECA right IP | 0,80 (0,67; 0,85) | 0,82 (0,68; 0,90) | 0,73 |
| ECA left IP | 0,75 (0,72; 0,93) | 0,75 (0,70; 0,82) | 0,69 |
| VA right IP | 0,66 (0,64; 0,71) | 0,64 (0,60; 0,73) | 0,55 |
| VA left IP | 0,61 (0,59; 0,65) | 0,69 (0,65; 0,74) | 0,04 |
| CCA right Pi | 2,10 (1,50; 2,20) | 1,39 (1,10; 1,40) | 0,15 |
| CCA left Pi | 1,47 (1,30; 1,50) | 1,52 (1,34; 1,58) | 0,48 |
| ICA right Pi | 1,39 (1,38; 1,50) | 1,30 (0,94; 1,40) | 0,42 |
| ICA left Pi | 1,03 (0,91; 1,10) | 1,35 (1,12; 1,60) | 0,04 |
| ECA right Pi | 2,20 (1,94; 2,40) | 2,26 (1,65; 2,90) | 0,90 |
| ECA left Pi | 1,60 (1,50; 1,78) | 1,85 (1,71; 2,10) | 0,009 |
| VA right Pi | 1,53 (1,50; 1,64) | 1,30 (1,16; 1,55) | 0,19 |
| VA left Pi | 1,05 (0,99; 1,20) | 1,21 (1,20; 1,26) | 0,32 |

The evaluation of cerebral hemodynamics was performed using doppler of cerebral arteries on the device of General Electric Company LOGIQ 9 (USA). The research was conducted on day 1 (№1) and day 7 (№2) from the beginning of treatment. In the course of the work, the registration of such indicators was carried out: systolic, diastolic and averaged linear velocity of blood flow (LVB), peripheral vascular resistance index (RI by L. Pourcelot) and pulsation index (PI by RG Gosling) in common carotid arteries (CCA), external carotid arteries (ECA), internal carotid arteries (ICA), and in the extracranial segments of the vertebral arteries (VA). Among the quantitative parameters of the cerebral blood flow, the following parameters were analyzed: peak systolic velocity (Vp), index of peripheral resistance by the method of L. Pourcelot (IR), pulsation index by the method of R.G. Gosling, (Pi). Based on the analysis of volumetric blood flow parameters from the internal carotid and vertebral arteries, we evaluated the total cerebral blood flow (CBF), which corresponds to the volumetric velocity in the internal carotid and vertebral arteries on both sides. Blood flow of the hemisphere (specific volume velocity of blood flow (ml/min) per 100 g brain substance – CBF/100 g) can be calculated by the formula CBF/100 g=CBF/13, if you take the average mass of the brain for 1300 g [6].

Statistical processing of the results was carried out using methods of variation statistic and using a program StatSoft «Statistica» v. 6.0. The parametric criterion t Student was used for normal distribution, the non-parametric Mann-Whitney U test, was used – in its absence, the Wilcoxon matched pairs test – to determine significant changes in the dynamics of inside the group. The statistical significance of the difference between the comparative values was considered probable at $p<0.05$.

## RESULTS

In the analysis of the studied parameters of cerebral hemodynamics during treatment with 0.9% NaCl, clinical interest caused a statistically significant reduction in peak systolic blood flow velocity in right-hand vertebrate segment arteries ($p=0.04$) and increase in the index of peripheral resistance in the right VA segments ($p=0.03$), all other study indices did not significantly change during

**Table III.** Dopplerography of extracranial cerebral arteries under the influence of treatment of AIS HES 130

| Indexes | Examination | | p |
|---|---|---|---|
| | №1 | №2 | |
| | HES 130 | | |
| CCA right Vp | 59 (54; 63) | 62 (58; 74) | 0,71 |
| CCA left Vp | 57 (46; 86) | 53 (50; 65) | 0,90 |
| ICA right Vp | 47 (41; 62) | 55 (48; 74) | 0,04 |
| ICA left Vp | 51 (34; 64) | 51 (41; 64) | 0,93 |
| ECA right Vp | 55 (53; 69) | 59 (53; 64) | 0,90 |
| ECA left Vp | 62 (59; 69) | 62 (54; 72) | 0,92 |
| VA right Vp | 45 (23; 56) | 43 (38; 64) | 0,90 |
| VA left Vp | 53 (32; 62) | 40 (32; 60) | 0,53 |
| CCA right IP | 0,70 (0,56; 0,71) | 0,63 (0,58; 0,72) | 0,62 |
| CCA left IP | 0,75 (0,63; 0,76) | 0,70 (0,54; 0,80) | 0,53 |
| ICA right IP | 0,67 (0,55; 0,70) | 0,57 (0,52; 0,71) | 0,71 |
| ICA left IP | 0,61 (0,59; 0,65) | 0,55 (0,49; 0,70) | 0,39 |
| ECA right IP | 0,78 (0,77; 0,81) | 0,79 (0,73; 0,81) | 1,00 |
| ECA left IP | 0,77 (0,76; 0,83) | 0,83 (0,80; 0,83) | 0,58 |
| VA right IP | 0,62 (0,60; 0,72) | 0,65 (0,47; 0,67) | 0,90 |
| VA left IP | 0,59 (0,52; 0,69) | 0,58 (0,52; 0,68) | 0,71 |
| CCA right Pi | 1,40 (0,92; 1,90) | 1,26 (1,09; 1,42) | 0,80 |
| CCA left Pi | 1,78 (1,20; 2,60) | 1,76 (1,17; 2,80) | 0,90 |
| ICA right Pi | 1,34 (0,84; 1,48) | 1,09 (0,78; 1,60) | 0,90 |
| ICA left Pi | 1,10 (1,05; 1,39) | 0,92 (0,80; 1,38) | 0,39 |
| ECA right Pi | 1,89 (1,50; 2,10) | 2,10 (1,90; 2,60) | 0,25 |
| ECA left Pi | 2,35 (1,77; 2,70) | 1,89 (1,56; 2,70) | 0,48 |
| VA right Pi | 1,26 (1,10; 1,80) | 1,30 (0,95; 1,60) | 1,00 |
| VA left Pi | 1,02 (0,80; 2,70) | 1,20 (0,92; 1,32) | 0,71 |

the first and second examinations (p>0.05) (table I).

Analysis of cerebral blood flow during treatment with mannitol showed a statistically significant decrease in peak systolic blood flow velocity in the right ICA (p=0.02), increase in the index of peripheral vascular resistance (by L. Pourcelot) in the segments of the left VA (p=0.04); the pulsation index (according to R.G. Gosling) of the left ICA (p=0.04) and the left ECA (p=0.009). All other researched indicators did not go beyond the normative indicators determined in healthy subjects [6] and did not change under the influence of infusion therapy with mannitol (p>0.05) (table II).

The results of the study showed that under the influence of infusion therapy with the solution of HES 130, a significant increase in peak systolic blood flow velocity in the right ICA was determined (p=0.04). All other studied parameters during treatment with this solution did not change (p>0.05) (table III).

The results of the dopplerography of group of patients with AIS receiving HAES-LX-5% solution indicate that there was a significant increase in the peak systolic blood flow velocity in the basins of the right ECA (p = 0.02), the left ECA (p = 0.03), the right ICA (p = 0.01), the left segments of VA (p = 0.04). All other studied parameters during treatment with this solution did not change (p> 0.05) (table IV).

The results of the study of hemisphere cerebral blood flow (CBF/100) caused significant academic and clinical interest. It was found that during the conduct of seven-day infusion therapy 0.9% NaCl and mannitol, a tendency to decrease CBF/100, respectively, for 0.9% NaCl by 2.8% (p>0.05) and for mannitol by 7.5% (p>0.05). While in the treatment of HES 130, the CBF/100 increases by 14.2% (p>0.05), and when applied HAES-LX-5%, the CBF/100 increases by 43.2% (p = 0.004).

## DISCUSSION

One of the main methods available for evaluation of cerebral circulation in patients with AIS is the ultrasound examination of blood supply to the brain, which enables to evaluate: the function of local and central mechanisms of vascular regulation, reserve capabilities of the cerebral circulation system associated with the presence of AIS, the effectiveness of treatment AIS [6 ] Determination of the

**Table IV.** Dopplerography of extracranial cerebral arteries under the influence of treatment of AIS HAES-LX-5%

| Indexes | Examination | | p |
|---|---|---|---|
| | №1 | №2 | |
| | **NaCl 0,9%** | | |
| CCA right Vp | 61 (56; 71) | 76 (70; 84) | **0,02** |
| CCA left Vp | 60 (53; 64) | 65 (64; 76) | 0,03 |
| ICA right Vp | 44 (38; 56) | 59 (51; 86) | **0,01** |
| ICA left Vp | 40 (33; 68) | 50 (38; 75) | 0,45 |
| ECA right Vp | 68 (47; 76) | 63 (50; 87) | 0,72 |
| ECA left Vp | 65 (55; 96) | 65 (58; 91) | 0,87 |
| VA right Vp | 43 (38; 45) | 43 (41; 57) | 0,53 |
| VA left Vp | 36 (30; 47) | 43 (39; 59) | **0,04** |
| CCA right IP | 0,75 (0,69; 0,78) | 0,74 (0,71; 0,79) | 0,72 |
| CCA left IP | 0,71 (0,69; 0,76) | 0,70 (0,69; 0,74) | 0,87 |
| ICA right IP | 0,65 (0,59; 0,69) | 0,62 (0,59; 0,66) | 0,87 |
| ICA left IP | 0,60 (0,53; 0,64) | 0,63 (0,52; 0,69) | 0,80 |
| ECA right IP | 0,79 (0,74; 0,86) | 0,80 (0,74; 0,83) | 0,95 |
| ECA left IP | 0,75 (0,69; 0,84) | 0,73 (0,71; 0,81) | 0,79 |
| VA right IP | 0,69 (0,52; 0,74) | 0,68 (0,58; 0,71) | 1,00 |
| VA left IP | 0,66 (0,59; 0,72) | 0,63 (0,60; 0,77) | 0,62 |
| CCA right Pi | 1,69 (1,38;1,84) | 1,72 (1,49; 1,98) | 0,57 |
| CCA left Pi | 1,35 (1,11; 1,72) | 1,49 (1,29; 1,75) | 0,38 |
| ICA right Pi | 1,24 (0,91; 1,79) | 1,22 (0,90; 1,59) | 0,79 |
| ICA left Pi | 1,09 (0,79; 1,26) | 1,10 (0,77; 1,33) | 0,80 |
| ECA right Pi | 2,16 (1,84; 2,68) | 2,30 (1,88; 2,85) | 0,64 |
| ECA left Pi | 2,34 (1,32; 2,72) | 1,50 (1,28; 2,76) | 0,95 |
| VA right Pi | 1,40 (0,87; 1,67) | 1,30 (0,95; 1,80) | 0,90 |
| VA left Pi | 1,22 (0,95; 2,12) | 1,45 (1,09; 1,80) | 0,80 |

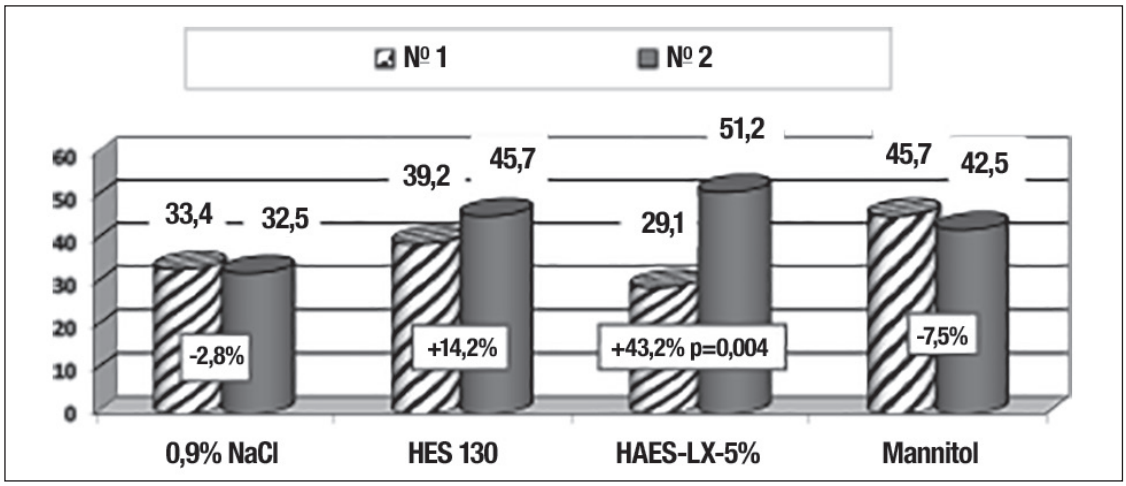


**Fig. 1.** Dynamics CBF/100 in different treatment groups on the 1st and 2nd day of the study

optimal composition of infusion in patients with AIS is a priority task intensive care of such patients [7].

Patients with AIS who received HES 130 determined a statistically significant increase in peak systolic blood flow velocity in the right ICA, which was not accompanied by changes in peripheral vascular resistance. This may be partly due to the improvement of the rheological properties of the blood, endothelial-protective effects of HES 130 [8].

In patients with AIS, a significant increase in peak systolic blood flow velocity was observed under the influence of

HAES-LX-5% therapy in the basins of the right ECA, left ECA, right ICA, left extracranial and intracranial segments of the VA and in the absence of peripheral resistance changes. Such correlations of dopplerography cerebral blood flow, in our opinion, can serve as a marker for increasing cerebral perfusion without signs of significant hypervolemia.

The analysis of quantitative parameters of cerebral blood flow during treatment with mannitol solution in patients with AIS showed a statistically significant decrease in peak systolic blood flow velocity in the right ICA and increase in the index of peripheral vascular resistance of the left VA, pulsation index of the left ICA and the left ECA. Lowering the speed of CBF in conditions of growth of peripheral vascular resistance can be evidence of hypovolemia and lead to cerebral hypoperfusion [6, 7]. Undoubtedly, hypoperfusion of the brain with acute stroke negatively affects the course of the disease and potentiates the development of complications, including fatal cases [9]. The results of the study do not contradict the data of evidence medicine, which shows a negative impact of planned using of mannitol in patients with AIS [3, 4].

When calculating CBF/100, it was found that in groups with 0.9% NaCl and mannitol, a tendency towards a decrease in cerebral blood flow, which could cause brain hypoperfusion, was determined. The cerebral blood flow did not increase significantly in patients who were treated with HES 130. When we used HAES-LX-5% for treating of AIS, the growth of cerebrovascular blood flow became statistically reliable, which contributed to the improvement of blood circulation in penumbra and the brain collaterals. The obtained data are completely consistent with the data we have received about the effect of the above-mentioned infusion solutions on the dynamics of neurological deficits in patients with AIS, where the data obtained are fully consistent with the dynamics of cerebral circulation [10].

## CONCLUSIONS

1. Seven-day infusion therapy with isoosmolar 0.9% NaCl and hyperosmolar mannitol solution 15% in patients with AIS showed a tendency to decrease cerebral blood flow, respectively -2.8% (p> 0.05) and -7.5% (p>0.05).
2. Seven-day use in patients with AIS of colloid-isoosmolar solution GEK 130 contributed to an increase in cerebral blood flow by +14.2% (p>0.05), colloid-hyperosmolar solution HAES-LX-5% by +43.2% (p=0.004).
3. The therapeutic effect that was obtained from infusion therapy with the investigated solutions is the basis for the study of the protective effect of infusion drugs of other groups in AIS.

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*Authors declare no conflict of interest.*


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