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TOPICAL ASPECTS OF INFUSION THERAPY

Summary. *Infusion therapy (IT) has been one of the main instruments of influence on homeostasis in critical conditions of different nature. Currently, IT is an essential component of anesthetic and intensive care. However, improper restoration of fluid balance was a major cause of mortality in intensive care units and postoperative intensive care in the 80's of the 20th century. Administration of any infusion media is an intervention into the internal environment of the body, which affects in a greater or lesser degree the performance of water-salt metabolism, acid-base balance, and osmolarity. Therefore, the clinicians are advisable to take into account the basic concepts of water-electrolyte metabolism, and their changes under the influence of IT, information about the function and dysfunction of the vascular endothelium, the properties of different intravenous fluids and hemodynamic monitoring capabilities to control the adequacy of IT. So called colloid osmotic pressure (COP) of plasma or oncotic pressure produced by plasma proteins is of great importance for the water retention and displacement. According to some researchers, COP is the main factor determining the transport of water between the tissues and capillaries. When volume corrector infusion is prescribed, the value of their COP should be considered. The study was conducted to find changes in COP of plasma in connection with surgery and ongoing IT. The surgery itself causes extravasation of fluid, and administration of intravenous fluids significantly increases this movement. Crystalloid infusion to patients during abdominal surgery resulted in a decrease in cardiac output in half of them. It is believed that the creation of intravascular normovolemia during surgery protects the endothelial glycocalyx (EG) from the influence of inflammatory mediators, minimizes pathological changes during transcapillary exchange between fluid and proteins by maintaining EG. A restrictive regimen of intravenous fluid administration significantly reduces the risk of postoperative complications. In surgical patients at high risk, targeted controlled infusion therapy is suitable.*

Currently, there is no complete understanding of the pathophysiology of increased vascular permeability and microcirculation disorders in sepsis. In addition, there is a lack of adequate endpoints of fluid replacement therapy in the studies. Researches on the clinical use of Sorbilact and Reosorbilact, carried out in leading Ukrainian clinics of surgical, trauma, therapy, oncology, obstetrical, pediatric, infectious and other profiles, have demonstrated the safety and efficacy of these drugs for detoxifying and antishock therapy; their opportunities in the treatment of diseases associated with severe impaired microcirculation, blood coagulation, energy, metabolic and other disorders have been proved.

Key words: *crystalloids, colloids, infusion therapy.*

Infusion therapy (IT) has been and remains one of the main instruments of influence on homeostasis in critical conditions of different nature. It is IT that takes a leading role in elimination of disorders associated with different critical conditions, and it is IT that is charged with the tasks aimed at elimination of metabolic, water-electrolytic, microcirculatory and other homeostatic disorders associated with different diseases. Currently, IT is an essential component of anesthetic and intensive care. However, improper restoration of fluid balance was a major cause of mortality in resuscitation units and postoperative intensive care in the 80's of the 20th century [1]. But at the present day, the perioperative infusion therapy remains one of the most debated subjects.

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The debates in respect of quantity and quality of solutions administered during major surgeries are still in progress [2, 24, 31, 41]. There are published works describing cases of extreme intravascular volume of iatrogenic genesis developed in the postoperative period, which led to complications and increase in postoperative mortality [3, 44, 45]. Researchers believe that the reason of the inadequate IT may relate, on the one hand, to the absence of optimal infusion medium that could be administered safely in required quantities, and on the other hand, to the absence of adequate control over physiological and biochemical parameters exerting influence on infusion media as well as difficulties in making complex evaluation of such parameters.

The "Mechanicalism" has frequently developed in the medical practice of routine administration of infusion media, and theoretical principles of their use are forgotten. Administration of any infusion medium is an intervention into the internal environment of the body, which affects in a greater or lesser degree the performance of water-salt metabolism, acid-base balance, and osmolarity. Therefore, the clinician is advisable to take into account the basic concepts of water-electrolyte metabolism, and their changes under the influence of IT, information about the function and dysfunction of the vascular endothelium, properties of different intravenous fluids and opportunities of hemodynamic monitoring to control the adequacy of IT.

The human organism tends to permanency of water-electrolyte homeostasis, primarily of its main constants — major electrolyte concentration, osmolarity, pH, normal hydration of fluid compartments. Electrolyte movement in the fluid compartment obeys the physiological laws, namely: laws of electroneutrality and isoosmolarity. Osmotic blood pressure is one of the most strictly determined parameters of the body internal environment.

Osmolarity is a total osmotic concentration of the kinetically active particles dissolved in 1 liter of solvent (mOsm/l). Normally, its value for blood is within 280 – 295 mOsm/l. Main components of plasma osmogramm are as follows: sodium, chlorine, bicarbonate, urea, glucose, and other cations and anions.

According to the law of isoosmolarity, there is the same osmotic pressure in all body fluid compartments having free water exchange. There is a semipermeable membrane between fluid compartments, which is a very important structural and functional unit of fluid, electrolyte and acid-base homeostasis that is characterized by free permeability for water and some components dissolved in it (for example, urea) and complicated permeability for other substances.

The main fluid media of the body are distributed in three water sectors or compartments: intravascular, interstitial (intercellular) and intracellular. There is an intensive exchange of fluids and all sorts of molecules between these compartments based on such physicochemical phenomena as diffusion and osmosis.

So called colloid osmotic pressure (COP) of plasma or oncotic pressure produced by plasma proteins is of great importance for the water retention and displacement. COP is often confused with the osmolarity, however, it accounts only to 1/150 of osmolarity (about 2 mOsm/l), and it is formed by macromolecular protein particles and is expressed, as a rule, in millimeters of mercury (25 mm Hg). The "Colloid" refers to large gel-forming molecules with a molecular weight above 10,000 Da. 80% of plasma COP is produced by albumin, 16-18% of COP is produced by globulins and 2% – by proteins of the blood coagulation system [4]. Thus, COP or oncotic pressure is a part of osmotic pressure produced by colloid molecules non-filterable through a capillary wall. According to some researchers, the plasma COP is, in particular, the main factor determining transport of water between tissues and capillaries as endothelial permeability is high for inorganic ions and for polymeric ions including proteins - it is low (normal) and increases in pathology [5, 6].

Endothelial cells of the vascular membrane have three surfaces: non-thrombogenic (luminal), adhesive (albuminal) and cohesive (contact). The luminal surface facing the vessel lumen is a non-thrombogenic surface and it is void of electron-dense connective tissue substance, but it has a complex and multicomponent, primarily carbohydrate-protein, system that is named endothelial glycocalyx (EG) [7].

According to the concept of "double protective layer" of the vascular wall, EG is the first barrier standing for its protection. The EG composition is determined by the group of proteoglycans, glycoproteins and glycosaminoglycans. There is marked out a group of membrane proteoglycans (bound to the membranes of endothelial cells of syndecans and glypicans) and a group of soluble proteoglycans (perlecan, biglycan, versican, decorin, mimecan). There is a dynamic balance between soluble components of EG and flowing blood, which allows to isolate the endothelial surface layer that is about 1 μm thick and it fixes about 1 liter of blood plasma. Owing to its complexity and localization on the line of blood circulation system, EG takes part in

the maintenance of vascular homeostasis.

It is a molecular filter that detains proteins and increases oncotic pressure in the endothelial surface layer [8]. Localization of EG on the strategic boundary between blood flow and vascular endothelium determines its influence on the fluid distribution between tissues and vascular system, i.e. fluid filtration through the vascular barrier is determined by the oncotic pressure gradient within the endothelial surface layer [9].

The classical concept suggesting that the main factor determining intravascular volume is the action of oppositely directed forces - hydrostatic and COP of intra- and extravascular fluids – undergoes change. It is exactly differences between data on theoretical calculations of fluid filtration in the microvessels and empirical findings that confirm the existence of EG [10]. In the course of previously conducted in vitro evaluations of filtration parameters (in accordance with Starling Principle) [8] basing on difference between hydraulic pressure and COP in the vessel lumen and adjacent tissue as well as basing on hydraulic conductivity of the vessel wall, the presence of protein (due to its low concentration in tissues) has been disregarded and venous fluid reabsorption and presence of lymph flow have not been taken into account [10]. That is why the classical concept of Starling has been transformed into a "double barrier concept": vascular barrier comprises of cohesive (contact) surface of endothelial cells and EG endothelial surface layer. Filtration properties of a capillary wall are determined by the presence of EG fibrous porous matrix on its endothelial surface (over transendothelial channels and intercellular junction areas) [8].

When volume corrector infusion is prescribed, the value of their COP should be considered. There was evaluated alteration of plasma COP associated with surgery and IT administration. There was observed reduction of plasma COP in dogs not receiving any infusion therapy during ovariohysterectomy [4]. There was confirmed reduction of plasma COP in early postoperative period in patients receiving infusion of crystalloid solutions [5]. On the other hand, hyperoncotic conditions may lead to cellular dehydration, hypervolemia and reduction in glomerular filtration rate [11].

Neither hydrostatic pressure nor plasma oncotic pressure correlates to transcapillary filtration during damage of capillary wall [12].

At the same time, Daniel Chappell et al. [13] recommend to apply infusion of colloids in particular, which will decrease capillary leakage even in damaged vascular barrier, in order to maintain normovolemia in tissue ischemia and endotoxinemia. Thus, COP is an important factor having impact on treatment outcomes in the postoperative period and in the intensive therapy.

Perioperative reduction of COP is associated with the loss of blood and its correction with hypooncotic solutions, as well as with the catabolic phase of the protein metabolism, and with increased permeability of vessel walls in tissue hypoxia and acidosis. The researchers associate this perioperative extravasation with damage of EG, which acts as an initial molecular filter forming an effective oncotic gradient within small space [5, 14].

The difference of hydrostatic pressure and oncotic pressure of blood and space under the endothelial glycocalyx rather than under the interstitium is of crucial importance when speaking about transcapillary fluid exchange [14]. It has been established that bolus administration of colloids increases extravasation of plasma protein in patients with intact cardiovascular and respiratory systems [14].

In hypervolemia, about 60% of administered colloid volume passes directly into the interstitial space. That is why colloid loading of a patient before development of the expected hypovolemia is considered to be problematic [15].

Inflammation mediators and atrial natriuretic peptide released in iatrogenic hypervolemia are engaged in the perioperative EG lesion. And thus, it is impossible to avoid in its entirety such the lesion and interstitial edema. Nevertheless, the most rational approach is the maintenance of a normal volume of blood circulation (VBC) free of hypervolemic peaks [16]. Clinical studies have proven that reduction of intravenous infusion volume in the perioperative period leads to a considerable decrease in incidence of such postoperative complications as anastomotic leak, pulmonary edema, pneumonia and wound infection [17 – 19]. At that, the restriction group mostly received colloids while the "free" group received crystalloids [18, 20].

It has been established that weight growth of patients in the resuscitation and intensive care unit (RICU) conditioned by the accumulation of extravascular fluid, clearly correlates to the prolongation of mechanical ventilation (MV) duration, vasopressor support, incidence of acute renal failure (ARF) and to the mortality [21].

The pathophysiological mechanism of colloid extravasation in intact vascular barrier requires clarification. The healthy glycocalyx must maintain the normal permeability, for colloids as well. Damage of the EG endothelial layer increases permeability resulting in the development of interstitial edema in patients with the

severe endothelial dysfunction associated not only with the trauma and inflammation but also with the hypervolemia. Destruction of the endothelial surface layer leads to the restoration of hydrodynamics by the classical Sterling's formula but under conditions of high interstitial COP, which causes the catastrophic tissue edema [16].

Infusion therapy in the perioperative period is one of the debatable topics relating to patient management. Fluid overloading worsens the treatment outcomes in large intestine surgery [22].

The surgery itself causes extravasation of fluid, and administration of intravenous fluids significantly increases this movement. The crystalloid infusion to patients during abdominal surgery resulted in a decrease in cardiac output in half of them [23].

It is believed that the creation of intravascular normovolemia during surgery protects the endothelial glycocalyx (EG) from the influence of inflammatory mediators, minimizes pathological changes during transcapillary exchange between fluid and proteins by maintaining EG. A restrictive regimen of intravenous fluid administration significantly reduces the risk of postoperative complications. Targeted controlled infusion therapy is reasonable for surgical patients at high risk [24 – 26].

Daily routine practice of an anaesthesiologist and a doctor of the intensive care unit comprises of prevention and correction of acute damages in the oxygen transport system links determined by the following clinical correlates: hypoxia (a respiratory link), shock (a circulatory link) and loss of blood (a hematic link) [1].

The shock is a circulatory-metabolic syndrome, in which oxygen delivery (tissue perfusion) does not satisfy the metabolic demand of tissues. It is worth noting that hypoperfusion plays the most important role in the conjugate pair "circulation — metabolism" as metabolic rate in various critical states may increase by 4-5 times without development of the shock clinical picture [1].

The septic shock relates both to relative and to absolute hypovolemia. The cascade of inflammatory reactions involving various mediators results in the damage of EG, the increase in permeability of microcirculatory vessels and in capillary leakage, which, in its turn, leads to accumulation of interstitial fluid, protein loss and tissue edema [27]. The hypoalbuminemia is developed causing the reduction of the intravascular COP, which worsens even more the ability to preserve the intravascular volume. Due to the above, sepsis and septic shock are characterized by reduction of preloading on the heart and decrease in cardiac output resulting in arterial hypotension, tissue perfusion disturbance and organ oxygenation followed by organs dysfunction.

Infusion therapy with crystalloid or colloid solutions in septic shock and sepsis accompanied by capillary leakage remains the point in question. According to Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock, 2012, there is foreseen a refusal from colloid plasma substitutes administration in patients with severe sepsis and septic shock [28]. The refusal was motivated by the results of multicenter studies aimed at the determination of the risk of acute renal injury and cases of excessive bleeding and at the assessment of survival of patients with severe sepsis and septic shock in case of resuscitation with usage of colloid plasma substitutes or only crystalloid solutions.

There are several studies offering not alternative but differentiated approach to the infusion therapy of sepsis and septic shock [29]. It is reasonable to perform fluid resuscitation with crystalloid solutions for patients with abdominal sepsis having initially not more than 10 points on APACHE II scale. Also it is recommended to perform fluid resuscitation with crystalloid and synthetic colloid solutions based on hydroxyethyl starch (HES), 6% HES 200/0.5 or 6% HES 130/0.42, for patients having initially more than 10 points on APACHE II scale. The use of colloid plasma substitutes at a dose of 15 ± 2 ml/kg leads to improvement of cardiac efficiency, organ blood flow, and microcirculation, decrease in intra-abdominal pressure, inhibition of capillary leakage without increase of the risk of acute renal injury and excess bleeding as well as reduces the risk of development of multiple organ failure [29].

Currently, there is no complete understanding of the pathophysiology of increased vascular permeability and microcirculation disorders in sepsis. In addition, there is a lack of adequate endpoints of fluid replacement therapy in the studies [30 – 32].

An adequate monitoring of fluid replacement in critical patients, in particular in patients with sepsis, is still an unsolved problem. The assessment of preloading is one of the key issues in respect of the haemodynamics monitoring. Fluid replacement in sepsis is intended for increase of the preloading in order to reach the maximum increase of cardiac output. Appropriateness of evaluation of the filling pressure, pulmonary artery wedge pressure, measured using catheter in the pulmonary artery and central venous pressure, was doubted [30].

At present, there are quite a lot of highly specific and effective techniques of hemodynamic status monitoring measuring the central haemodynamics, namely: arterial transpulmonary thermodilution, esophageal Doppler spectroscopy, LidCO and PulseCO technologies, thermodilution, pulse wave analysis (PiCCOplus) and others [33].

Stroke volume variation may be a dynamic parameter of the response to volemic loading. Fluid responsiveness concept allowed to develop a differentiated approach to the volume therapy. It has been established that cardiac output (CO) after volemic loading increases only in about half of patients (volume-sensitive patients). The rest of them, according to Frank–Starling mechanism, have no increase in CO and administration of fluid in such patients is useless or even dangerous as it can cause pulmonary edema [33].

Currently, in order to predict fluid responsiveness, i.e. increase of CO in response to fluid infusion, stroke volume variation (SVV) provoked by mechanical ventilation is a subject undergoing evaluation. As of today, SVV is a value, which is automatically calculated and monitored via minimal invasive monitors of the central haemodynamics. SVV is not an indicator of the volemic status and not a marker of cardiac preloading, it is sooner an indicator of a position on Frank–Starling curve. Patients on the plateau have low SVV (less than 12%) and the volume loading does not lead to a substantial increase of CO. And vice versa, patients on the steep curve (sensitive to the cyclic changes of preloading provoked by the mechanical ventilation) have high SVV (more than 12%) and the volume loading leads to a substantial increase of CO [33]. In the situations when it is impossible to use SVV, a trial administration of 250 ml of fluid for a short period of time with constant monitoring of stroke volume and CO may be used for volume loading efficiency control.

Thus, delivery of a target-based therapy allows to reach an optimal ratio of oxygen delivery/consumption in critically ill patients.

Venous blood saturation is the gold standard in respect of determination of global adequacy of oxygen transport and oxygen need. This parameter may be taken for trigger when making a decision of CO increase. In order to determine the volume of fluid infusion necessary for a patient, it is recommended to take into account haemodynamics indices (AP, pulse pressure variations, CO, central venous pressure), indices of diuresis and arterial and central venous blood gases [34].

It goes without saying that there is no ideal plasma substitute (not only at the present moment but in principle). In this respect, the main task for an intensivist is to combine in the optimal way infusion media of different groups and develop rational infusion-transfusion programs basing on the advantages and disadvantages of the drug products and a general state of each patient.

From a clinical point of view, when prescribing crystalloids within any infusion-transfusion program, the following peculiarities of such products should be taken into consideration: absence of colloid osmotic pressure resulting in the shift of fluid in the extracellular space; prompt renal elimination; restricted volemic effect and its low duration; complexity of hypovolemia replenishment exceeding 30%; risk of interstitial space overflow resulting in pulmonary edema and hypoxia and edema of brain and peripheral tissues.

Crystalloids obviously prevail when there is required a correction of minor or moderate hypovolemia (blood loss of not more than 20% of VBC, as a rule, does not demand colloid administration), as well as in combination of hypovolemia and different variants of dehydration and hypoelectrolytic status. There are higher diuretic effect, low allergenic potential, considerably weaker, as compared to colloids, impact on hemostasis and systemic inflammatory cascade and low cost among undisputed advantages of crystalloids.

With respect to saline solutions there are two important peculiarities determining the specificity of their administration, namely: degree of balance and content of alkaline reserve carriers. The concept of balance characterizes a degree of conformity of a solution composition with the water-electrolytic balance of normal plasma and extracellular fluid. Physiological salt solution is considered to be the least balanced solution. In most of cases, more balanced solutions occur to be more preferable. However, in case of hyperkalemia, hypercalcemia, and particularly in hypochloremic metabolic alkalosis, it is exactly physiological salt solution that is more preferable as a replacement medium [1].

Content of alkaline reserve carriers is another important property of polyelectrolytic solutions that determines the specificity of indications, contraindications and dose regimen. These are substances, which, in the course of metabolism, form hydrogen carbonate replenishing in such a way the buffer capacity of hydrocarbonate blood system (lactate, acetate, malate, and fumarate). Infusion of solutions free of alkaline reserve carriers causes a loss of buffer blood capacity and leads to development of

hemodilutional acidosis. Infusion media with high content of alkaline reserve carriers are contraindicated in alkalosis and severe liver impairment.

Among colloid solutions, when speaking about multifunctionality of activity, there is no alternative to natural colloid — albumin — which molecular weight amounts to about 69,000 Dalton. Approximately two thirds of this protein form a constantly renewing compartment localized in the interstitial space. Albumin moves from intravascular space into interstitial returning into vessels via lymphatic system. Such a movement is evaluated basing on the half-life (normally it is ranged within 16 — 18 hours) and rate of transcapillary leakage [30]. 5% albumin solution is isotonic, its COP amounts to 20 mm Hg and it remains within the intravascular space on the condition that the capillary membrane is not altered. 20% and 25% albumin solutions are hyperoncotic; their COP amounts to 80 — 100 mm Hg, and thus, they have the property to increase intravascular volume due to fluid attraction from the interstitial space. Findings of the recent analytical studies have completely rehabilitated albumin as a volume corrector of critical states (and, from our point of view, once more time raised the question on validity of the evidence based medicine itself) [35].

Among synthetic colloids, HES products are the absolute leaders both in the world and in Ukraine for the last two decades. Currently, with respect to colloid blood substitutes, it is generally recommended to use HES solutions of the latest generations, namely tetrastarches (140/0.4). Advantages of HES include an ability to increase substantially plasma oncotic pressure and stabilize haemodynamics and, at the same time, to provoke minimum number of adverse reactions in contrast to dextrans or protein products. However, the risk of development of renal function impairment when using starches is constant and dose-dependent [30].

An active substance of colloids based on modified fluid gelatin (MFG) is a partially hydrolyzed and succinylated gelatin (average molecular weight is 30,000 — 35,000 Da). The increase in VBC and rise of AP occur not only due to administered solution but also due to additional inflow of intertissue fluid into the bloodstream (volemic coefficient is about 100%). Among domestic products of this group of colloids, there is presented Volutenz — a solution of 4% succinylated gelatin dissolved in a balanced solution (Ringer's acetate) with an average molecular weight of 30,000 Da. Theoretical osmolarity is not more than 273 mOsm/l. MFG solutions, in particular Volutenz, owing to their molecular weight and COP, which is equal to that of the solution of human albumin (33 mm Hg), exhibit sufficient duration of volume activity — up to 3–5 hours. Principle route of excretion is renal. Duration of Volutenz hemodynamic effect amounts to 3–4 hours. Maximum daily dose is 200 ml/kg. Provoking osmotic diuresis, MFG products ensure maintenance of renal function under shock conditions. They reduce blood viscosity, improve microcirculation and reduce the likelihood of development of interstitial edema. A substantial advantage of plasma substitutes based on MFG is their relatively weak influence on hemostasis system and structural segments of nephrons. That is why MFG solutions, with respect to safety, prevail over HES products in congenital coagulopathies, development of severe disorders of coagulation system and severe renal injuries. However, it is recommended to monitor respective parameters and record obtained data when determining dose regimen of any volume expander in patients with blood-clotting disorders, renal insufficiency and chronic liver diseases [30].

There were used dextrans for infusion therapy for several decades. Dextran is a hydrophilic polysaccharide, a glucan, which is synthesized from sucrose by Leuconostoc mesenteroides bacteria. Dextrans may have varying polymerization degree due to which solutions based on them have different molecular weights and functional purposes. Volemic properties of dextrans are rather high, and the fact that at the present time HES products have considerably pressed dextrans by no means relates to a low volume-replacing activity of the latter but to higher incidence of severe complications and adverse reactions [30].

At present, polyatomic alcohols, such as mannitol, sorbitol and xylitol, which, due to their properties and absence of toxic effect, are used in medicine for quite a long time, have been ingrained in the practice of infusion therapy.

Mannitol administered intravenously is scarcely metabolized, promptly leaves the blood stream, is distributed within extracellular space and is excreted with urine by glomerular filtration. The main indication of mannitol administration is a therapy of cerebral edema and intracranial hypertension (IH) in a craniocerebral trauma (CCT). Recommended doses vary from 0.5 to 2.0 g/kg every 6 hours. However, there has been recently described a large number of complications and restrictions in the course of its administration. The most important restriction is the plasma osmolarity, which must not exceed 320 mOsm/l. The volume of interstitial fluid in the brain amounts

to 320–340 ml. This volume expands by more than 50% in the areas with impaired permeability of the blood-brain barrier (BBB). However, mannitol acts only on a "healthy" brain, i.e. it has a dehydrating effect mainly in areas with preserved BBB and where formation of osmotic gradient between capillary and interstitial space is possible. In mannitol administration, there is a high probability of development of a rebound phenomenon, i.e. change of a phase of prompt reduction of intracranial pressure to a phase of cerebral blood flow enhancement. Mannitol penetrating through the blood-brain barrier may accumulate in brain tissues and provoke rebound effect (increase of intracranial pressure after initial reduction). But the most frequent complications of mannitol administration are as follows: hypotension, sudden reduction of VBC (due to diuretic effect), increase of haematocrit and worsening of rheological properties of blood, and hyperosmolar state. Recently, mannitol has been recommended for patients with IH, when it is necessary to gain time for performance of surgical decompression, prevent or suspend the developing brain herniation.

Complex infusion products - Reosorbilact and Sorbilact — perfectly do for solving infusion therapy problems. Both products contain sorbitol, main cations (Na+, K+, Ca2+, Mg2+), Cl anion and lactate anion. Total osmolarity of Reosorbilact is by three times higher than that of blood plasma (900 mOsmol/l) and of Sorbilact — by 5.5 times higher (1,670 mOsmol/l). Owing to hyperosmolalilty, Reosorbilact and Sorbilact provoke fluid inflow from intercellular space into the blood stream, which is accompanied by increase of VBC due to plasma volume expansion. They improve microcirculation and tissue perfusion. Owing to the pronounced specific osmotic diuretic effect of sorbitol associated with the absence of natural mechanisms of reabsorption of polyatomic alcohols in the proximal renal tubules, there is observed a pronounced diuretic action of both products, especially of Sorbilact. In addition, sorbitol, partially metabolized to fructose, contributes to normalization of carbohydrate and energy metabolism. Sorbitol stimulates fatty acid oxidation via non-ketogenic metabolic pathway and contributes to easier usage of ketone bodies within Krebs cycle.

Researches on the clinical use of Sorbilact and Reosorbilact, carried out in leading Ukrainian clinics of surgical, trauma, therapy, oncology, obstetrical, pediatric, infectious and other profiles, demonstrated the safety and efficacy of these drugs for detoxifying and antishock therapy; proved their opportunities in the treatment of diseases associated with severe impaired microcirculation, blood coagulation, energy, metabolic and other disorders [1]. Clinical effects of infusion media with high content of sorbitol were studied in details in trauma and neuro-surgical clinic during treatment of patients with a polytrauma. At present, Sorbilact and Reosorbilact are the drug products of choice in prevention and treatment of cerebral edema after cerebral tumor surgeries [36]. It has been proven that the rebound syndrome is not that pronounced if these products are used. In comparison with mannitol, Reosorbilact and Sorbilact have other advantages associated with the ability to eliminate metabolic acidosis, maintain electrolyte composition of the blood, and cover energy demands of cells (additional anti-edema factors). Moreover, there has been proven the efficacy of Sorbilact administration not only after tumor surgeries but also after surgeries associated with haematoma (craniocerebral trauma, hemorrhagic stroke), inflammatory processes (brain abscess, serous meningoencephalitis), as well as during conservative management (ischemic stroke due to thromboembolism of the middle cerebral artery) [37, 38]. It has been proven that complex application of L-lysine aescinat 10.0-20.0 ml and Reosorbilact or Sorbilact at a dose of 10 ml/kg is efficient in treatment of cerebral edema [37]. It is recommended as a basis for infusion therapy both in the preoperative and in the intra- and postoperative periods to administer Reosorbilact at a dose ranged from 3–5 to 7–10 ml/kg in combination with L-lysine aescinat 10.0–20.0 ml (in children — 0.15 — 0.2 ml/kg) in the course of complex anesthetic management of patients with neuro-surgical pathology [37, 38].

Primary and secondary brain damages are developing in acute cerebral insufficiency (ACI). The main secondary brain damages are hypoxia and hypotension. Hypotension occurs due to development of hypovolemia, low cardiac output, reduction of preloading and low total peripheral resistance. But, in the pronounced hypovolemia, normal values of AP and HR may be maintained only against high peripheral resistance. Application of aggressive tactics of infusion therapy allowed to avoid the development of secondary cerebral ischemic damages in 72% of patients [39].

IH may develop into cerebral stroke in patients with severe craniocerebral trauma. That is why it is quite often necessary to use the hyperosmolar solutions. In severe brain lesion and hyperthermia, it is necessary to administer a

large amount of fluid and sympathomimetics in order to maintain central perfusion pressure (CPP) against impaired cerebral circulation autoregulation. Cerebral blood flow and CPP in impaired autoregulation of cerebral vessels depend on systemic AP. Systemic haemodynamics monitoring allows to determine degree of hypovolemia, modify the structure of infusion therapy and increase the volume of administered colloids.

Recently, there have been conducted major randomized controlled studies on usage of colloid and crystalloid solutions in intensive therapy of acute cerebral insufficiency [40, 42, 43]. The authors compared administration of 6% and 10% HES 130/0.4 with administration of a crystalloid solution for four and more days in patients with acute ischemic stroke. No efficiency and safety differences between two groups have been revealed [40, 43]. Therefore, it is required to conduct additional prospective randomized controlled studies [43].

In general, it is rather difficult to distinguish effects of infusion media on neurological outcomes from effects on cardiovascular system. Causes of myocardium dysfunction after brain lesion could be numerous. They include vasoconstriction of the pulmonary vasculature associated with the brain lesion and extracerebral disorders, usage of sedative drug products in high doses as a component of intracranial hypertension therapy. In addition, stress-induced cardiomyopathy is observed in such patients. In this context, hypervolemia in the course of infusion therapy may lead to severe myocardium dysfunction and cardiopulmonary complications regardless of a type of used solution [43, 44].

Application of goal-oriented hemodynamic correction intended for optimization of cardiac output and water status in early stages of medical treatment of patients with ACI should be accompanied by improved clinical outcomes and decrease in cardiopulmonary complications versus traditional treatment. A next generation innovative infusion drug product under the trade name Gecoton (a multicomponent balanced colloidal hyperosmolar solution), which fully complies with the requirements set for an ideal volume expander, was developed in Ukraine. On the one hand, the obtained hyperosmolar solution induces an increase of plasma osmolarity and fluid shift from cells and interstitium into the blood stream (a hyperosmolar component), and on the other hand, it ensures plasma oncotic pressure increase and preservation of the intravascular volume (a colloid component). The main active substances of the product are HES 130/0.4, xylitol and sodium lactate. Gecoton exhibits hemodynamic, rheological, antishock and disintoxication effects. HES administration restores impaired haemodynamics, improves microcirculation and blood rheological properties (owing to reduction of haematocrit), reduces blood viscosity, lowers platelet aggregation and prevents red blood cell aggregation. Xylitol is a pentatomic alcohol that is metabolized in liver (80%) and tissues of other organs (kidneys, heart, pancreas, adrenal gland, and brain) and excreted with urine. Xylitol takes part in the phosphogluconate cycle of metabolism, does not cause the reduction of adenine nucleotides (ATP, ADP, AMP) in the liver and exhibits more potent antiketogenic and nitrogen-preserving effects as compared with glucose. Taking into account that xylitol is a source of energy with metabolism independent of insulin, it exhibits antiketogenic and lipotropic activity. Maximum disposal rate of xylitol amounts to 0.25 g/kg/h. Sodium lactate is used as an alkaline reserve carrier. The timing of the onset of sodium lactate action is 20–30 minutes post administration.

The mechanism of action of Gecoton is as follows: emergence of osmotic gradient between intra- and extracellular spaces; volume redistribution from intracellular space, interstitium, endothelium and red blood cells into the blood stream; primary activation of capillary blood flow; fluid shift along an osmotic gradient; prompt replenishment of VBC; restoration of hemodynamic balance and stabilization of haemodynamics; continuance and intensity of volemic effect; improvement of microcirculation, tissue perfusion and tissue oxygenation.

In 2013–2014 we carried out a study in the anaesthesiology and intensive care unit of Public Municipal Institution "Clinical Mine Hospital" [47]: In the course of the study we administered Gecoton in patients with ischemic stroke and in patients with a concomitant injury including CCT with a cerebral contusion.

The group 1 (15 patients with ischemic stroke and 10 patients with a concomitant injury) received mannitol at a dose of 1–2 g/kg as the basic anti-edema therapy; haemodynamics and cerebral blood flow volume were maintained owing to administration of balanced ionic solutions (Sterofundin, Ionosteril) at a dose of 2–4 ml/kg/h under diuresis rate control (not less than 2 ml/kg/h), infusion of mesatonum was administered when required.

The group 2 (15 patients with ischemic stroke and 10 patients with a concomitant injury) received Gecoton at a dose of 3–4 ml/kg/day as the basic anti-edema and infusion therapy; haemodynamics and cerebral blood flow volume were maintained owing to administration

of balanced ionic solutions (Sterofundin, Ionosteril) at a dose of 0.5–1.0 ml/kg/h under diuresis rate control (not less than 2 ml/kg/h).

There were taken dynamic measurements of the following parameters: central haemodynamics (CH) by rheography method (systolic AP, total peripheral resistance (TPR), cardiac index (CI), stroke volume index (SVI)), cerebral hemodynamics by a transcranial dopplerography, osmolarity before and after drug product administration by calculation method.

The presence at baseline of normal- or hypodynamic type of hemodynamic was the key criterion for patient inclusion into the study. Gecoton/mannitol was administered for the first 3 days of the therapy along with monitoring of cerebral edema severity level. Thereafter, there was added L-lysine aescinat.

There was revealed that in order to reach targeted indices of CH and cerebral blood flow in the group 1, it was required to apply hypervolemia strategy with sympathomimetics administration, which, in certain cases, led to the development of peripheral oedema and additional administration of diuretics. The mentioned strategy led to the positive dynamics of linear blood flow rate values, which was more pronounced on the lesion side.

In the group 2, owing to Gecoton administration and application of volemic loading of restrictive type, targeted indices of central haemodynamics were reached without usage of sympathomimetics, and the dose of crystalloids demanded for stabilization of haemodynamics was decreased by 3 times without reduction of diuresis rate. We managed to reach the improvement of cerebral blood flow on the lesion side statistically not distinguishable from that of the group 1, which was characteristic both of anti-edema and positive hemodynamic effects of Gecoton. The presence of xylitol in the drug product contributes to decrease in incidence of acute cerebral edema, which has favourable effect on cerebral haemodynamics indices.

When standard fluid and anti-edema intensive therapy was applied in patients whether with acute cerebrovascular disease or with a concomitant injury, significant regress of neurologic symptomatology up to 12 points by Glasgow Coma Scale was reached by the 5th day. The significant regress of neurologic symptomatology in patients who received modified therapy (Gecoton + infusion therapy of restrictive type) was also reached by 5th day.

Thus, application of different schemes of infusion and anti-edema therapy resulted in improvement of indices of central haemodynamics and cerebral blood flow. Gecoton administration allowed to avoid unnecessary hypervolemia in most of cases (infusion therapy of restrictive type) and significantly decrease the frequency of sympathomimetic usage.

The obtained results allow to recommend administration of Gecoton in the treatment scheme of patients with acute cerebral insufficiency. Revealed anti-edema effect of Gecoton is comparable with that of mannitol in patients with ACI.

In 2013–2014 we carried out the second study on Gecoton usage in 40 patients with various pathologies in the intensive care unit of DOKTMO. 28 patients out of 40 underwent abdominal surgeries (small and large intestine, gallbladder, pancreas etc.), 7 patients underwent soft tissue surgeries, 2 patients had lung surgeries and 3 patients had carbon monoxide poisoning. Patient inclusion criteria were as follows: hypodynamic type of haemodynamics at baseline, absence of sings of renal insufficiency and impaired coagulation. Gecoton administration was included into complex infusion therapy in order to correct hypodynamic type of blood circulation and haemodilution. A low dose of the preparation — 3 ml/kg/day — was administered. Average infusion rate amounted to 1.5 ml — 3.0 ml/kg/h. Administered dose of the drug product for three days running did not exceed 600-800 ml. The total volume of infusion-transfusion therapy amounted on the average to 1.2–1.5 L per day and included additional solutions of crystalloids and glucose. Patients underwent three-day follow-up control of the following parameters: central haemodynamics by rheography method, acid-base balance, blood gases, Ht, SpO2, coagulation profile (activated partial thromboplastin time, prothrombin time, thrombin clotting time, platelets, and soluble fibrin monomer complexes). Conducted studies resulted in revelation of tendencies towards changes of observed parameters (acid-base balance, blood gases, Ht, and coagulation profile). CH values (AP, SVI, CI) on admission were decreased by 15–20%, and TPR and HR values were increased by 18 and 24% respectively versus values of the control group. Repeated follow-up examinations revealed restoration of evaluated CH parameters up to control level in 32 patients in 12 hours and in 8 patients in 18 hours starting from the treatment initiation. There was no patient with hypodynamic blood circulation in 72 hours starting from the treatment initiation. The obtained results allow to recommend administration of Gecoton in the complex treatment of patients with hypodynamic blood circulation aimed at stabilization of blood circulation and curative therapeutic blood dilution (haemodilution).

The urgent issue of emergency IT is the quickness of hemodynamic effect onset (for maximum prompt restoration of main functions of vital organs and systems) as well as its duration. It is important to remember that transfused fluids are considered to be

medicinal products, and thus, their administration should be well-considered and justified [45]. The common sense based on the results of numerous studies and personal experience convince clinicians that combination of crystalloids and semisynthetic colloids is an ideal combination for IT in severe diseases and critical conditions [46].

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АКТУАЛЬНІ АСПЕКТИ ІНФУЗІЙНОЇ ТЕРАПІЇ

Резюме. Інфузійна терапія (ІТ) була одним із головних інструментів впливу на гомеостаз у різних критичних ситуаціях. У даний час ІТ є важливим компонентом анестезії та інтенсивної терапії. Однак неправильне відновлення балансу рідини було основною причиною смертності у відділеннях інтенсивної терапії та післяопераційної інтенсивної терапії в 80-х роках XX століття. Призначення будь-яких інфузійних середовищ є втручанням у внутрішнє середовище організму, що більшою чи меншою мірою впливає на показники водно-сольового обміну, кислотно-лужного стану, осмолярності. Тому лікарі повинні враховувати основні параметри водно-електролітного обміну і їх зміни під впливом ІТ, дані про функціонування та дисфункції судинного ендотелію, властивості різних рідин для внутрішньовенного введення і можливості моніторингу гемодинаміки для контролю адекватності ІТ. Велике значення в підтримці рівня води та її переміщенні має так званий колоїдно-осмотичний тиск (КОТ) плазми, або онкотичний тиск, що створюється білками плазми. На думку деяких дослідників, КОТ є основним фактором, що регулює рух води між тканинами та капілярами. При призначенні інфузії волюмкоректорів необхідно враховувати величину їх КОТ. Дослідження було проведено з метою виявлення змін КОТ плазми у зв'язку з хірургічним втручанням і безперервною ІТ.

Операція сама по собі викликає екстравазацію рідини, а внутрішньовенне введення рідини значно посилює це переміщення. Кристалоїдні інфузії під час хірургічного втручання на органах черевної порожнини призводять до зниження серцевого викиду в половини хворих. Вважається, що створення внутрішньосудинної нормоволемії під час операції захищає ендотеліальний глікокалікс (ЕГ) від впливу медіаторів запалення, мінімізує патологічні зміни при транскапілярному обміні рідини та білків шляхом збереження ЕГ. Обмежувальний режим внутрішньовенного введення рідини значно зменшує ризик післяопераційних ускладнень. У пацієнтів хірургічного профілю з групи високого ризику доцільна цілеспрямована контрольована інфузійна терапія.

У даний час немає повного розуміння патофізіології підвищеної проникності судин і мікроциркуляторних порушень при сепсисі. Крім того, проведено недостатньо адекватних досліджень щодо вивчення замісної інфузійної терапії. У дослідженнях із клінічного використання Сорбілакту та Реосорбілакту, проведених у провідних українських клініках хірургічного, травматологічного, терапевтичного, онкологічного, акушерського, педіатричного, інфекційного та інших профілів, показано безпеку та ефективність цих препаратів при детоксикації та протишоковій терапії; доведені їх можливості при лікуванні захворювань, пов'язаних із тяжкими порушеннями мікроциркуляції, згортання крові, енергетичними, метаболічними й іншими розладами.

Ключові слова: кристалоїди, колоїди, інфузійна терапія.

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TOPICAL ASPECTS OF FLUID THERAPY

Summary. Infusion therapy (IT) has been one of the main instruments of influence on homeostasis in critical conditions of different nature. Currently, IT is an essential component of anesthetic and intensive care. However, improper restoration of fluid balance was a major cause of mortality in intensive care units and postoperative intensive care in the 80s of the XX century. The administration of any infusion media is an intervention into the internal environment of the body, which affects in a greater or lesser degree the performance of water-salt metabolism, acid-base balance, osmolarity.

Therefore, the clinician is advisable to take into account the basic concepts of water-electrolyte metabolism, and their changes under the influence of IT, information about the function and dysfunction of the vascular endothelium, the properties of different intravenous fluids and hemodynamic monitoring capabilities to control the adequacy of IT. So called colloid osmotic pressure (COP) of plasma or oncotic pressure produced by plasma proteins is of great importance for the retention and displacement water. According to some researchers, the COP is the main factor determining the transport of water between the tissues and capillaries. When volume corrector infusion is prescribed, the value of their COP should be considered. Study was conducted to find changes in COP of plasma in connection with surgery and ongoing IT.

The surgery itself causes extravasation of fluid, administration of intravenous fluids significantly increases this movement. Crystalloid infusion to patients during abdominal surgery resulted in a decrease in cardiac output in half of them. It is believed that the creation of intravascular normovolemia during surgery protects the endothelial glycocalyx (EG) from the influence of inflammatory mediators, minimizes pathological changes during transcapillary exchange between fluid and proteins by maintaining EG. Restrictive regimen of intravenous fluid administration significantly reduces the risk of postoperative complications. In surgical patients at high risk, targeted controlled infusion therapy is suitable.

Currently, there is no complete understanding of the pathophysiology of increased vascular permeability and microcirculation disorders in sepsis. In addition, there is a lack of adequate endpoints of fluid replacement therapy in the studies. Researches on the clinical use of Sorbilact and Reosorbilact, carried out in leading Ukrainian clinics of surgical, trauma, therapy, oncology, obstetrical, pediatric, infectious and other profiles, demonstrated the safety and efficacy of these drugs for detoxifying and antishock therapy; proved their opportunities in the treatment of diseases associated with severe impaired microcirculation, blood coagulation, energy, metabolic and other disorders.

Key words: crystalloids, colloids, fluid therapy.