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New opportunities for correction of water and electrolyte homeostasis disordersin critical conditions

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Water-electrolyte imbalance occurs in 66.78% of patients in critical condition. We examined 60 patients who were treated in the General ICU of the Municipal Institution "Kyiv Regional Clinical Hospital", aged between 18 and 60 years. Patients were divided into two groups: 1st group included patients with severe concomitant injury and 2nd-3rd degree traumatic shock (n=30), in which a standard intensive therapy (IT) has been supplemented with Rheosorbilact at dose of 8-10 ml/kg of body weight, with a parallel correction of detectable hypomagnesemia and hypophosphatemia; 2nd group included patients with concomitant injury and 2nd-3rd degree traumatic shock (n=30) that undergone the standard intensive therapy.

Application of polyionic multicomponent, sorbitol-based solutions leads to rapid stabilization of hemodynamic parameters, it is not accompanied by disruption of homeostasis, and promotes the elimination of acid-base imbalance. Treatment with solutions based on sorbitol is well tolerated and is not accompanied by the development of complications associated with the use of colloidal solutions or classical crystalloid.

Key words: water-electrolyte exchange, infusion therapy, sodium, potassium, magnesium, phosphorus, sorbitol.

In patients in critical conditions, the disorders of water-electrolyte homeostasis are registered rather frequently. Recently, it was shown that water-electrolyte imbalance occurs in 66.78% of patients in critical condition, while azotemia – in 20%, and hypoglycemia - in 13.33% of patients [1]. In this regard, an adequate, rationally designed infusion therapy acquires a great importance.

Infusion therapy in the treatment of patients in critical conditions is performed in order to eliminate hypovolemia, fluid-electrolyte and acid-base imbalances, abnormalities of blood rheology and hemostasis correction, disorders of microcirculation and metabolism, to ensure the effective oxygen transport and detoxification. It has a multifaceted impact on the basic life support systems of the body. At the same time the volemic, rheological and hemodilution effects are observed.

Crystalloid and colloid infusions are used as basic infusion medium. Isotonic electrolyte solutions by their composition are similar to the extracellular fluid, but have little direct volemic effect (not more than 20% of the injected medium) [2, 3]. In recent years, among the colloidal solutions increasingly popular become hydroxyethyl starch solutions (HES) due to the high volume effect and long half-life with a relatively small number of side effects. [4]

In recent years, increasingly frequent are publications about the benefits of therapy for acute circulating blood volume deficiency and shock by so called low-volume infusion therapy. It consists in combined intravenous administration of hypertonic electrolyte solution (e.g., 7.5% NaCl solution) and colloidal blood substitute solution for fixing the effect of interstitial fluid movement into vessels [2, 5].

This infusion program contributes to the primary activation of capillary blood flow during mobilization of fluid from the swollen endothelial cells, erythrocytes and the interstitium into the bloodstream through the creation of an osmotic gradient between these cells, interstitium and blood

plasma. At the same time, the use of hypertonic solutions of sodium chloride can lead to severe violations: negative inotropic effect, hyperosmolar state and cellular dehydration [2,3]. Quantity of administered crystalloid solutions should be large enough to maintain the necessary circulating blood volume and cardiac output, while only 20% of administered volume remains in the bloodstream. The remaining volume after 30 minutes passes into the interstitial space, leading to compression of capillaries and microcirculation disorder. Furthermore, most of the salt solutions are not physiologic, and used in large volumes for correction of volemic disorders, they may lead to the fluid-electrolyte and acid-base disorders.

Their negative properties have led to the development of balanced electrolyte solutions, such as Plasmalyte-148, Ionosteril, Sterofundin, Rheosorbilact which also contain the alkaline reserve donators.

One of the most promising ways of correcting the volemic conditions disorders is a "low-volume" infusion with hyperosmolar combined polyelectrolyte balanced solution Rheosorbilact ("Yuria-Pharm", Ukraine). The prospectivity of its application as a first-line drug in hypovolemic shock is obvious – balanced by potassium, calcium and magnesium composition, sodium which is contained in two salts (chloride and lactate), provides an osmolarity in range of 600 mOsm/l, and sorbitol (300 mOsm/l) in isotonic concentration – provide total osmolarity of 900 mOsm/l, 3 times exceeding the plasma osmolarity. It induces a quite rapid, within 1 hour, inflow of fluid from the intercellular space to the bloodstream, enabling the improvement of microcirculation and tissue perfusion, which in turn leads to circulating blood volume expansion by plasma, resulting in autohemodilution. Alkaline reserve donator (sodium lactate) has a neutral reaction, in the bloodstream it dissociates into sodium ions and lactic acid, which is metabolized in the liver to sodium bicarbonate, which increases the reserve and titratable alkalinity of the blood. Along with it the correction of metabolic acidosis goes on slowly without acute fluctuations in blood pH, unlike the effects of sodium bicarbonate. Sorbitol, which is used in this concentration, is not reabsorbed by the renal tubules, due to the lack of natural mechanisms of reabsorption of polyatomic alcohols in the proximal renal tubules in humans, which conditions on its osmotic effect and a significant diuretic effect [6].

Thus, the theoretical perspective of Rheosorbilact use in infusion therapy of volemic disorders is evident [6-8].

In addition to the above-described volemic disorders, critically ill patients very frequently have disruption of electrolytes exchange. This increases the risk of arrhythmias, neuromuscular transmission disorders; the regulation of body fluids and biologically active substances complicates. The problem complicates by the fact that the practice of intensive care unit (ICU) in most of cases is a routine determination of only three "main" electrolytes – sodium, potassium, chlorine. However, our own observations and literature data indicate the lack of due attention to the level of such important elements as magnesium and phosphorus in blood. At the same time, changes in the balance of these elements result in a substantial disruption of homeostasis [9].

Thus, Magnesium ranks second after potassium in its physiological importance. It is a necessary component of catalytic reactions of nearly 300 enzyme systems. Magnesium contributes to the formation and hydrolysis of ATP, creatine phosphate; plays an important role in glycolysis; it is included in various steps of the citrate cycle, oxidative phosphorylation; it is involved in activation of phosphatases, nucleases, peptidases. Magnesium regulates the secretion of parathyroid hormone and neuromuscular transmission. Hypomagnesemia is often accompanied by increased excitability of the central nervous system, and hypermagnesemia – by CNS depression [10].

Decrease of magnesium concentration in the blood serum to less than 1 mEq/l causes hypomagnesaemia. It can develop as a result of:

• intestinal malabsorption (e.g., diarrhea, steatorrhea);

• as a result of increase of magnesium losses with the urine (e.g., in the case of osmo-diuretics and furosemide use, or hyperglycemia background);
• on the intake of ethanol, aminoglycoside antibiotics, amphotericin B, pentamidine, digitalis, cyclosporine or cisplatin [11].

Phosphorus takes part in the processes of glycolysis and energy production by ATP synthesis. Most of the phosphorus in the body is contained in the form of organic compounds – phospholipids and phosphoproteins. Decrease of the phosphorus content in the blood serum below the normal level (0.8 mmol/l) emerges hypophosphatemia (HPE).

Reduction of plasma phosphate levels is always accompanied by energy production disorder in all cells, where the aerobic glycolysis prevails. HPE leads to displacement of the hemoglobin dissociation curve to the left (increases the affinity of hemoglobin with oxygen), which deteriorates the oxygen return to tissues by hemoglobin. One of the manifestations of energy production oppression in the presence of hypophosphatemia is muscle weakness. Hypophosphatemia may also cause respiratory muscle weakness [12].

Hypophosphatemia and hypomagnesemia is often observed in patients with craniocerebral injury due to polyuria inducted by mannitol [13] and in patients with diabetic ketoacidosis due to increased release of phosphate and magnesium with urine, and its relocation into a cell together with glucose and potassium [14]. It should be emphasized that the clinical symptoms of hypomagnesemia and hypophosphatemia are nonspecific, and yet leading to fatal complications described in the literature [9,15].

Thus, the modern approach to the treatment of disorders of water and electrolyte homeostasis in critically ill patients should include the use of complex polyionic solutions, as well as the identification and elimination of electrolytes metabolism disorders, including magnesium and phosphorus. In order to verify this thesis, we conducted the following study.

Material and methods: We examined 60 patients who were treated in the General ICU of the Municipal Institution "Kyiv Regional Clinical Hospital", aged between 18 and 60 years.

Patients were divided into two groups: 1st group included patients with severe concomitant injury and 2nd-3rd degree traumatic shock (n=30), in which a common intensive therapy (IT) has been supplemented with Rheosorbilact at dose of 8-10 ml/kg of body weight, with a parallel correction of detectable hypomagnesemia and hypophosphatemia; 2nd group included patients with concomitant injury and 2nd-3rd degree traumatic shock (n=30) that undergone the common intensive therapy. These groups were representative by the main clinical, age and gender characteristics (Table 1).

Table 1

Characteristics of patients in the study groups and their distribution depending on the type of treatment and infusion therapy

Indicators	***1st group (n = 30)***	***2nd group (n = 30)***
Type of treatment	Common + Rheosorbilact + correction of magnesium and phosphorus metabolism	Common treatment
Age, years	43,6 ± 1,9	42,9 ± 2,7
Body weight, kg	84,7 ± 3,1	85,8 ± 4,2
Ratio, male / female	18/12	19/11

The average Rheosorbilact dose for patients in the intensive care units was 8-10 ml/kg per day (600-800 ml/day). Considering that Rheosorbilact is a hyperosmolar solution (around 900 mOsm/l), its

introduction was performed under the control of blood osmolarity level and was not administered in patients with confirmed or suspected diagnosis of hyperosmolar state. Besides, all patients with clinical premise of development of magnesium and phosphorus metabolic disorders were examined for the levels of magnesemia and phosphatemia. If the reduction of these indicators was identified, phosphate solutions (potassium or sodium phosphate) were included in therapy program. Magnesium solutions were administered only if a significant deficiency of this element in the blood was identified. In such cases 1 mEq of magnesium per 1 kg of body weight was administered for the first day and 0.5 mEq/kg/day for the following 3-5 days. However, in most clinical situations the additional administration of magnesium solutions was not required since polyionic solution Rheosorbilact included in the infusion therapy contains a dose of magnesium, which is sufficient to cover its medium and moderate deficit. All patients with plasma phosphate levels below 0.3 mmol/l received phosphorus medicines intravenously: sodium phosphate or potassium phosphate at rate of 0.6 mg (0.02 mmol)/kg/hr. In all cases the laboratory monitoring of electrolyte levels was carried out at least 1 time per day.

The study was performed in four stages: initially, after the infusion, in 12 and 24 hours after administration of the drug.

The common complex of intensive therapy was performed in all patients in both groups of the study. Respiratory support was performed until the sustainable stabilization of external respiration, blood gas and recovery of adequate cardiac pump function. If necessary, a vasopressor and inotropic support, analgosedation were applied. Packed red blood cells and fresh frozen plasma were included in the infusion-transfusion therapy, if indicated. The shifts of water-electrolyte balance, the acid-base balance and the indices of hemostatic system were amended.

We studied hemodynamic parameters (blood pressure (BP) systolic and diastolic, heart rate, central venous pressure), the parameters of the "red blood", the coagulation system, acid-base balance and blood gas. Dynamics of clinical and laboratory parameters allow to determine the efficacy and tolerability of the investigated plasma substitutes.

Statistical analysis of the research results was carried out using software packages Excel-2003 and Statistica 6.0.

Results and discussion: Analysis of hemodynamic parameters in the first group has shown a reduction by 5.7% in heart rate in the second stage of the study, and by 14.4% - in 24 hours after the infusion of Rheosorbilact. On the contrary, the systolic and diastolic blood pressure indices were respectively 15.2% and 20.5% higher in the second stage of the study, indicating the effective volemic CBV replenishment. These dynamics are also observed in the increase of central venous pressure (CVP) parameters, which was up 135.6% after infusion compared to initial values (Table 2).

Table 2 **Changes in hemodynamic parameters (M ± m)**

Indicator	*Group*	*Initially*	*After infusion*	*In 12 hour*	*In 24 hours*
Heart rate, beats / min	1	96,4±10,7	94,3±8,7	86,4±9,3	82,7±7,4*
	2	95,8±11,2	94,8±10,6	90,6±8,5	88,7±6,9*,**
Systolic blood pressure, Mm Hg	1	98,7±12,1	109,8±10,4	118,6±9,2*	116,7±8,8*
	2	99,4±10,7	104,6±11,7	106,8±14,7**	107,3±12,9**
Diastolic blood	1	56,9±7,8	65,6±10,9	74,6±8,9*	75,0±9,1*

pressure, Mm Hg	2	57,8±9,3	64,1±8,7	69,7±10,1**	72,3±8,8*
CVP, Mm Hg	1	2,1±0,9	25,8±6,4*	56,9±14,3*	72,6±19,4*
	2	4,7±0,8	20,6±14,4	38,9±19,6*,**	58,4±17,7*,**

Notes:
* - significance of differences in performance compared with the initial values ($p < 0,05$).
** - significance of differences in performance between groups ($p < 0,05$).

Analyzing the performance of "red blood" in both groups of the study we have ascertained the unidirectional changes in all patients. It was noted a significant decrease in hemoglobin level by 18.8%, and a tendency to decrease in hematocrit by 14.3% after 12 hours since the time of injury, which was associated with post-traumatic blood loss and hemodilution effect. A further increase in these indicators within the 24 hours of post-traumatic period was conditioned by the correction of the globular volume deficiency by introduction of packed red blood cells (Table 3).

Table 3 **Dynamics of some biochemical parameters (M ± m)**

Indicator	Group	Initially	After infusion	In 12 hour	In 24 hours
Hemoglobin, g/l	1	101,4±10,3	82,4±9,6*	94,7±6,9*	94,7±6,9*
	2	102,3±10,1	84,6±7,9*	90,7±11,9	90,7±11,9
Hematocrit, l/l	1	0,27±0,08	0,24±0,12	0,29±0,08*	0,29±0,08*
	2	0,28±0,07	0,22±0,11*	0,28±0,09*	0,28±0,09*
Prothrombin index,%	1	76,8±9,2	64,6±10,9*	68,3±9,9	68,3±9,9
	2	77,2±10,3	62,7±9,1*	60,8±7,8**	60,8±7,8**
Activated recalcification time, s	1	68,1±8,7	60,4±10,3*	72,6±19,4*	72,6±19,4*
	2	69,7±9,8	57,9±12,6*	62,4±9,7*,**	62,4±9,7*,**
Fibrinogen, g/l	1	3,2±0,4	2,8±0,3	3,1±0,5	3,1±0,5
	2	3,3±0,6	2,7±0,4	3,0±0,7	3,0±0,7
pH	1	7,19±0,05	7,36±0,09*	7,38±0,07	7,38±0,07
	2	7,18±0,09	7,26±0,07**	7,28±0,09**	7,28±0,09**

Notes:
* - significance of differences in performance compared with the initial values ($p < 0,05$).
** - significance of differences in performance between groups ($p < 0,05$).

Development of blood loss was also reflected in the reduction of blood coagulation system indices in patients of 1st group after 12 hours from the time of injury. So, prothrombin index (PTI) was lower by 15.8%, activated recalcification time – by 11.8%, fibrinogen – by 12.5% during the first 12 hours of observation compared to initial level, with subsequent normalization in the third stage of study, due to the transfusion of plasma and hemostatic therapy. Similar shifts of "red blood"

indicators were also noted in 2nd group patients. They had a more pronounced decrease in blood hemostasis at the second stage of the study by means of a significant reduction of PTI by 22.5%, tendency toward a reduction of activated recalcification time by 12% and fibrinogen – by 27.3% during the first 12 hours of observation, which indicated the depletion of clotting factors. At the third stage of the study it was marked a trend to increased levels of activated recalcification time by 5.9% and 3.4% in 1st and 2nd groups respectively. On the contrary, prothrombin index and fibrinogen level in the third stage tended to increase but did not reach the original level and were lower by 11.8% and 3.1%, respectively, in 1st group. In the 2nd group PTI was 2.6% lower than initially. Fibrinogen level in 2nd group was 27.5% higher compared to initial level. The above-mentioned changes in the indices of "red blood" and hemostasis were nonspecific, and we associated it with peculiarities of traumatic disease course, blood loss and correction of these shifts during the IT, which was reflected in the dynamics of growth of these indicators in the third stage of the study. We haven't noted any specific effect of Rheosorbilact on blood coagulation indicators in patients with polytrauma, which indicates the sufficient safety of the drug.

An important link of the response to trauma, blood loss, as well as quantitative and qualitative composition of infusion-transfusion therapy is the acid-base balance. The 1st group revealed the development of decompensated metabolic acidosis initially. Under the influence of IT already after 12 hours there was a trend towards normalization of pH level (7,36 ± 0,09). In the 2nd group after 12 hours of study a trend toward normalization of pH (7,26 ± 0,07) was observed, but after 24 hours the pH level in the 2nd group was still significantly lower than normal (7,28 ± 0,09). More rapid normalization of pH, in our opinion, is due to presence of solutions with reserve alkalinity source (lactate) in the infusion program for patients of the first group. Dynamics of blood gas composition in both groups in the study stages showed a trend toward normalization compared to initial level.

It should be noted that the described program of intensive therapy was generally well tolerated by patients. During the treatment there were detected no incidence of side effects typical for crystalloid use (swelling of the extremities, acute heart failure) or colloids (hypocoagulation, renal dysfunction). Levels of electrolytes deficiency quickly (within 2-3 days) returned to normal parameters.

Conclusions:

The modern approach to the treatment of water and electrolyte homeostasis disorders in critically ill patients should include the use of complex polyionic solutions, as well as the identification and elimination of disorders of electrolytes metabolism, including magnesium and phosphorus.

The use of polyionic multicomponent solutions based on sorbitol leads to the rapid stabilization of hemodynamic parameters, is not accompanied by disorders of homeostasis, and promotes the elimination of acid-base imbalance.

The treatment using the solutions based on sorbitol is well tolerated and is not accompanied by the development of complications associated with the use of colloidal solutions or classical crystalloid.

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წყლისა და ელექტროლიტების ჰომეოსტაზის დარღვევების ახალი საკორექციო საშუალება კრიტიკული მდგომარეობის დროს.

(კიევი,უკრაინა)

შესწავლილია კრიტიკულ მდგომარეობაში მყოფი 60 პაციენტი,რომლებსაც მკურნალობდნენ ზოგადი პროფილის კრიტიკული მედიცინის კლინიკაში.პირველი ჯგუფის მე-2-3 ხარისხის ტრავმულ შოკში მყოფ 30 პაციენტს,სტანდარტული მკურნალობასთან ერთად ეძლეოდა 8-10 მლ/კგ რეოსორბიტოლი..მეორე ჯგუფის იმავე პათოლოგიის მქონე 30 ავადმყოფს კი მხოლოდ სტანდარტული მკურნალობა ჩაუტარდა.სორბიტოლის ბაზაზე მომზადებული პრეპარატი ხელს უწყობდა სისხლისმიმოქცევის აღდგენას და მეტაბოლური აციდოზის კორექციას პირველი ჯგუფის პაციენტებში. მიუთითრბენ ამგვარი მკურნალობის გამოყენების მიზანსეწონილობას კრიტიკული მედიცინის კლინიკაში.