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The first data on international multicenter clinical study RheoSTAT-CP0620 on the efficacy and safety of Rheosorbilact® infusion in therapy of sepsis

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Conflict of interest: none

ABSTRACT. Sepsis stays a common and life-threatening pathological condition; hospital mortality in patients with sepsis exceeds 30 %. Fluid resuscitation is an important component of sepsis treatment. The purpose of this work was to evaluate the efficacy and safety of the multicomponent infusion solution Rheosorbilact in the treatment of patients with sepsis. The international multicenter randomized study RheoSTAT-CP0620 included 180 patients aged 18 to 60 years diagnosed with sepsis. Patients received Rheosorbilact therapy in dosage according to the package insert. A change in the SOFA score on day 3 of treatment was considered to be the primary endpoint. Changes in APACHE II, SAPS II, and MODS scores, as well as changes in endogenous intoxication markers on day 3 of treatment, were considered the secondary endpoints. The safety of the drug was assessed by analysis of adverse events and vital signs after 3 days of therapy. On day 3 of Rheosorbilact treatment, statistically significant changes in SOFA (by 2.01±1.37 points), APACHE II (by 4.24±3.76 points), SAPS II (by 3.40±5.30 points), and MODS (by 1.37±1.37 points) scales were recorded. In addition, there was a statistically significant improvement in markers of endogenous intoxication (urea, creatinine and total bilirubin concentrations, leukocyte counts, and calculated intoxication indices) on day 3 of treatment. The majority of adverse events (71.74 %) were mild. None of the adverse events were related to the study drug and did not result in the patient's withdrawal from the study. According to the results of RheoSTAT-CP0620, Rheosorbilact is an effective and safe drug for the treatment of patients with sepsis. It is advisable to include Rheosorbilact in routine treatment algorithms for patients with sepsis.

KEY WORDS: sepsis, infusion therapy, Rheosorbilact, intoxication, multiorgan failure.

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Перші результати міжнародного багатоцентрового клінічного дослідження RheoSTAT-CP0620 щодо ефективності та безпеки інфузійного розчину Реосорбілакт® у комплексній терапії сепсису

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РЕЗЮМЕ. Сепсис залишається поширеним і життєзагрозливим патологічним станом, госпітальна смертність за якого перевищує 30 %. Важливою складовою лікування сепсису є інфузійна терапія. Метою цього дослідження було оцінити ефективність і безпеку багатокомпонентного інфузійного розчину Реосорбілакт у терапії пацієнтів із сепсисом. У міжнародному багатоцентровому рандомізованому дослідженні RheoSTAT-CP0620 узяли участь 180 пацієнтів віком від 18 до 60 років із діагнозом сепсису. Пацієнти отримували терапію препаратом Реосорбілакт у дозуванні відповідно до інструкції для медичного застосування. Первинним показником ефективності терапії вважалася зміна оцінки за шкалою SOFA на 3-й день терапії. Як вторинні показники розглядалися зміни оцінки за шкалами APACHE II, SAPS II та MODS, а також зміна маркерів ендогенної інтоксикації на 3-й день терапії. Безпека препарату оцінювалася за допомогою аналізу небажаних явищ і життєво важливих показників через 3 дні терапії. На 3-й день лікування препаратом Реосорбілакт було зафіксовано статистично значущі зміни оцінки за шкалами SOFA (на 2,01±1,37 бала), APACHE II (на 4,24±3,76 бала), SAPS II (на 3,40±5,30 бала) та MODS (на 1,37±1,37 бала). Крім того, було виявлено статистично значуще покращення маркерів ендогенної інтоксикації (концентрації сечовини, креатиніну та загального білірубіну, кількості лейкоцитів і розрахункових індексів інтоксикації) на 3-й день лікування. Більшість небажаних явищ (71,74 %) були легкими. Жодне з небажаних явищ не було пов'язане з досліджуваним препаратом і не призвело до вибування пацієнта з дослідження. Згідно з отриманими результатами, Реосорбілакт є ефективним і безпечним препаратом для лікування пацієнтів із сепсисом. Дослідження RheoSTAT-CP0620 обґрунтовує доцільність включення препарату Реосорбілакт у рутинні алгоритми лікування пацієнтів із сепсисом.

КЛЮЧОВІ СЛОВА: сепсис, інфузійна терапія, Реосорбілакт, інтоксикація, поліорганна недостатність.

Первые результаты международного многоцентрового клинического исследования RheoSTAT-CP0620 по эффективности и безопасности инфузионного раствора Реосорбилакт® в комплексной терапии сепсиса

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Конфликт интересов: отсутствует

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РЕЗЮМЕ. Сепсис остается распространенным и жизнеугрожающим патологическим состоянием, госпитальная смертность при котором превышает 30 %. Важной составляющей лечения сепсиса является инфузионная терапия. Целью данной работы стала оценка эффективности и безопасности поликомпонентного инфузионного раствора Реосорбилакт в терапии пациентов с сепсисом. В международном многоцентровом рандомизированном исследовании RheoSTAT-CP0620 приняли участие 180 пациентов в возрасте от 18 до 60 лет с диагнозом сепсиса. Пациенты получали терапию препаратом Реосорбилакт в дозировке согласно инструкции для медицинского использования. Первичным показателем эффективности терапии считалось изменение оценки по шкале SOFA на 3-й день терапии. Как вторичные показатели рассматривались изменения оценки по шкалам APACHE II, SAPS II и MODS, а также изменение маркеров эндогенной интоксикации на 3-й день терапии. Безопасность препарата оценивалась посредством анализа нежелательных явлений и жизненно важных показателей через 3 дня терапии. На 3-й день лечения препаратом Реосорбилакт было зафиксировано статистически значимые изменения оценки по шкалам SOFA (на 2,01±1,37 балла), APACHE II (на 4,24±3,76 балла), SAPS II (на 3,40±5,30 балла) и MODS (на 1,37±1,37 балла). Кроме того, было выявлено статистически значимое улучшение маркеров эндогенной интоксикации (концентрации мочевины, креатинина и общего билирубина, количества лейкоцитов и расчетных индексов интоксикации) на 3-й день лечения. Большинство нежелательных явлений (71,74 %) были легкими. Ни одно из нежелательных явлений не было связано с исследуемым препаратом и не привело к выбыванию пациента из исследования. Согласно полученным в исследовании RheoSTAT-CP0620 результатам, Реосорбилакт является эффективным и безопасным препаратом для лечения пациентов с сепсисом. Целесообразным является включение препарата Реосорбилакт в рутинные алгоритмы лечения пациентов с сепсисом.

КЛЮЧЕВЫЕ СЛОВА: сепсис, инфузионная терапия, Реосорбилакт, интоксикация, полиорганная недостаточность.

Introduction

Sepsis remains a common and life-threatening pathological condition. Approximately 19 million people are diagnosed with sepsis each year [5, 6]. The significant prevalence of sepsis in our time can probably be explained by the increase in the prevalence of chronic diseases in the aging population, an increase in antibiotic resistance, as well as an increase in the frequency of invasive procedures, the use of immunosuppressive drugs and chemotherapy [18]. Despite significant improvements in medical care for critically ill patients, hospital mortality in sepsis exceeds 30 % [2-4].

According to the Third International Consensus on Definitions of Sepsis and Septic Shock (2016), sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is considered life-threatening based on an increase in the SOFA (Sequential [Sepsis-related] Organ Failure Assessment) score by ⩾2 points [3]. Early detection and rapid medical care in sepsis reduces morbidity and mortality.

Modern concept of sepsis treatment involves performing certain procedures at a certain time. In particular, after checking the state of the respiratory tract and stabilizing respiration, patients receive infusion therapy (IT), antibiotic therapy, lactate determination, and bacterial culture inoculation [10-13].

Since the invention of solutions for infusion, there has been a debate regarding which solution is optimal for patients in grave conditions [36]. Ideal for use in sepsis, the infusion product should increase intravascular volume without accumulation in tissues, have a plasma-like chemical composition, improve the effects of treatment and be economically feasible. Not every solution for infusion has all these properties, so the question of optimal IT in sepsis is still acute for clinicians.

Monocomponent solutions do not make it possible to implement all IT tasks in sepsis, so multicomponent infusion preparations are the basis of a current IT. Due to the urgency of this issue and the lack of an unambiguously recognized optimal solution for infusion, the aim of this work was to study IT in sepsis based on literature data and analyze the results of a phase IV randomized controlled trial (RCT) RheoSTAT-CP0620. This multicenter RCT was performed to evaluate the efficacy and safety of the multifunctional drug Rheosorbilact, which includes sorbitol (60 g), sodium lactate (19 g), sodium chloride (6 g), calcium chloride (0.1 g), potassium chloride (0.3 g), magnesium chloride (0.2 g) and water for injection (up to 1 liter). The osmolarity of the drug is 891 mOsm/l, pH – 6.0-7.6.

During the course of the study in patients with sepsis who received Rheosorbilact therapy, the dynamics of scores based on the integral scales SOFA, MODS (Multiple Organ Dysfunction), APACHE II (Acute Physiology And Chronic Health Evaluation II), SAPS II (Simplified Acute Physiology Score II) were evaluated by comparing the baseline indicator and the indicator on day 3 of treatment; vital indicators (body temperature, heart rate – HR, systolic and diastolic blood pressure – BP, respiratory rate); dynamics of changes in indicators of clinical and biochemical blood analysis, as well as blood gas composition.

Materials and methods

An electronic search in English-language sources of the PubMed database for the last 20 years using keywords "sepsis", "septic shock", "fluid resuscitation", "sepsis resuscitation", "infusion" was conducted. A review of the results of phase IV of the international multicenter open RCT RheoSTAT-CP0620 with a blinded assessment of the efficacy endpoints was also analyzed based on the report provided by "Yuria-Pharm". This study, which lasted from 07/10/2017 to 11/12/2019, was conducted by a contract research organization in accordance with the principles of Good Clinical Practice (ICH GCP), ethical standards of the Helsinki Declaration of the World Medical Association and national standards.

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The RheoSTAT RCT included 629 patients with sepsis, peritonitis, burn disease, and pneumonia who were treated in 37 clinical centers in 6 countries. The RheoSTAT-CP0620 sepsis sub-study involved 180 patients from 12 clinical centers in 5 countries – Ukraine, Moldova, Georgia, Uzbekistan and Kazakhstan. This sub-study included hospitalized adult patients of both genders with a verified sepsis diagnosis established no more than 24 hours prior to screening who met the inclusion criteria. The latter were the age of 18-60 years; the diagnosis of sepsis established according to ACCP/SCCM criteria; the time from the moment of diagnosis of sepsis to the screening visit – no more than 24 hours; signed informed consent to participate in the study; baseline SOFA score ⩾2 points.

The study included 180 patients, 89 of whom were randomized to the Rheosorbilact group. Data analysis was performed in several populations: 1) a population of all patients included in the study (intent-to-treat, ITT), which included all randomized patients who were prescribed and administered at least one infusion and who had data on the SOFA score both before and after this infusion (79/89 people, 88.76 %); 2) per protocol population (PP), which included all randomized patients who completed the study according to the protocol (completed the prescribed period of treatment and follow-up without significant deviations from the study protocol) (74/89 people, 83.15 %); 3) a safety population that included all randomized patients who received at least one infusion and at least one safety parameter assessment visit (89 people, 100 %). The main population for evaluation of the primary efficacy parameter was the ITT population.

Main group participants (n=89) received Rheosorbilact solution for infusion for 3 days by intravenous infusion at a dose of 200-400 ml/day according to the drug package insert. On day 3, their efficacy criteria were evaluated, and after 14±2 days, safety and disease outcomes were monitored (fig. 1).

It is worth noting a thorough and objective assessment of the efficacy and safety of the study drug, which was carried out on the basis of numerous evaluation scales, and clinical and laboratory indicators presented in table 1.

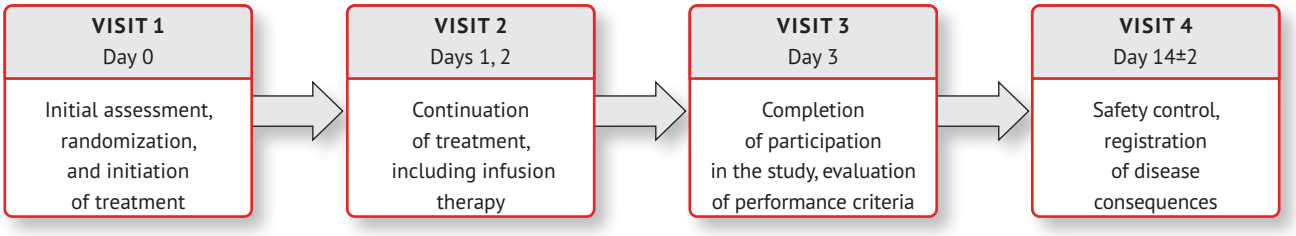

Fig. 1. RheoSTAT-CP0620 study design

Table 1. Criteria for efficacy and safety evaluation in the RheoSTAT-CP0620 study

Efficacy assessment was performed by comparing baseline values during hospitalization and baseline values on day 3 of therapy	
Primary Outcome Measures: change in the total score on the SOFA scale	**Secondary Outcome Measures:** • Change in the total score on the APACHE II, SAPS II and MODS scales • Assessment of endogenous intoxication based on: 1) biochemical markers: serum concentrations of glucose, lactate, pyruvate, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, gamma-glutamyltranspeptidase, medium and low molecular weight substances and medium molecular weight oligopeptides, albumin fraction, total and effective albumin concentration, albumin index of toxicity and binding ability, level of procalcitonin; 2) immunological criteria: quantitative content of leukocytes, lymphocytes, platelets with the calculation of leukocyte, nuclear and hematological indices of intoxication (II), ratio of neutrophils and lymphocytes, concentration of C-reactive protein, immunoglobulins, interleukins 1 and 2, complement components 3 and 4; 3) clinical signs (adynamia, apathy, weakness, memory and sleep disorders, irritability, anorexia), electrocardiogram parameters, indicators of central hemodynamics and assessment of consciousness on the Glasgow scale
Safety assessment	
• Overall frequency of adverse events (AE) • Frequency of serious AE • Frequency of AE associated with the use of the study drug • Frequency of AE that led to the patient's withdrawal from the study • Frequency of AE not previously described in the instructions for use of the study drug • Frequency of multiorgan failure • Overall survival of patients (%) during follow-up (day 14±2)	

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Results and discussion

For a long time, aggressive large-volume IT was considered the cornerstone of sepsis treatment [11]. This approach was based on the theory that septic shock is a form of hypovolemic shock and is therefore characterized by tissue hypoperfusion [14]. However, it turned out that aggressive large-volume IT inevitably leads to massive fluid overload. The dangers of this approach have been clearly demonstrated in three large multicenter RCTs – ProCESS, ARISE, and ProMISe [26, 27], but unfortunately, this tactic is still used in medical institutions. Current experimental, observational, and randomized clinical studies show that low-volume IT provides better clinical outcomes [14-17].

The recommendations of the Surviving Sepsis Campaign provide rapid administration of at least 30 ml/kg of crystalloid solution for hypotension or lactate content ⩾4 mmol/l, but although the recommendation has a strong status, the quality of its evidence base is low, i. e. this indication is based mainly on expert opinion [11].

The tactic of prescribing 30 ml of infusion solution per 1 kg of body weight has several significant drawbacks. First of all, the recommendations do not specify which body mass index should be used for calculations: actual, calculated, or ideal for a particular height. For example, if the actual weight indicator is used, then a patient weighing 150 kg should be injected with a liquid bolus with a volume of 4,500 ml, which is accompanied by a high risk of complications and mortality associated with hypervolemia, especially in the presence of heart or renal failure [20]. In addition, in the treatment of septic shock, it is rarely possible to accurately determine the patient's height and weight [28-30]. It should be noted that the standard approach of administration of 30 ml of fluid per 1 kg of body weight contradicts with the current paradigm of maximum individualization of any treatment, including IT [27, 31].

Therefore, the idea of large-volume IT is based on a misunderstanding of the pathophysiology of sepsis. In this concept, hypoperfusion is considered the central link in the disease pathogenesis. Typical signs of septic shock (increased blood lactate concentrations, oliguria, liver dysfunction, and impaired consciousness) were interpreted as consequences of hypoperfusion of the relevant organs, and an aggressive IT was designed to dramatically increase cardiac output, eliminating this hypoperfusion. Now it is known that such a concept is overly simplified and inaccurate. There is growing evidence that brain, heart, kidney, and liver dysfunction in sepsis is mainly caused by bioenergetic insufficiency, rather than microcirculatory dysfunction and impaired perfusion. This is confirmed by the fact that in patients with sepsis, the Frank – Starling curve shifts down and to the right, that is, in conditions of sepsis, the heart poorly reacts to fluid load [20]. In patients with septic shock, an aggressive IT causes a minimal increase in end-diastolic and stroke volume, but sharply increases the pressure in the left atrium with the subsequent development of pulmonary oedema and in the right atrium with a further increase in pressure in the liver and kidney veins, and therefore, the development of insufficiency of these organs [32]. Due to the increase in hydrostatic pressure in the pulmonary vessels and liver and kidney veins, the release of natriuretic peptides increases, and the fluid moves into the interstitial space, provoking tissue oedema. The latter, in turn, causes a violation of tissue microarchitecture, interferes with capillary blood flow and lymph outflow, disrupts intercellular interaction and slows down the diffusion of oxygen and metabolites [33, 34]. The spectrum of complications of large-volume IT includes impaired consciousness, brain and lung oedema, pleural effusion, impaired myocardial contractility, decreased glomerular filtration rate, uremia, impaired intestinal motor function, ascites, and impaired liver function [20]. Low-volume IT makes it possible to avoid these complications and improve the consequences for the patient [35].

In recent decades, the use of multicomponent infusion drugs has been the mainstay of IT. Among the sorbitol-containing medications, it is worth noting the complex infusion preparation of polyfunctional action Rheosorbilact ("Yuria-Pharm", Ukraine). In addition to sorbitol, it contains other important electrolytes, namely potassium, calcium, and magnesium. The chloride content in Rheosorbilact is only 112.7 mmol/l, which reduces the risk of hyperchloremic acidosis. An important component of this solution for infusion is sodium lactate, which provides an alkalizing effect, correcting metabolic acidosis, which often complicates severe infections, sepsis, peritonitis, intestinal obstruction, kidney failure, burns, shock, chronic hypoxia, etc. Rheosorbilact has a beneficial effect on heart function, tissue regeneration and respiratory function of blood, stimulates the functions of the mononuclear phagocyte system, has a detoxification effect, enhances diuresis, improves kidney and liver function. Successful experience of Rheosorbilact use for detoxification and normalization of rheological properties of blood in patients with severe purulent-inflammatory diseases, such as peritonitis [33], destructive pancreatitis [34], diabetic foot syndrome [35], suggests an improvement in clinical outcomes in case of sepsis.

In general, the presence of sorbitol and sodium lactate in the composition of Rheosorbilact, which can potentiate each other's detoxification properties, as well as correct the acid-base state and water-electrolyte balance, puts this drug on a par with powerful detoxification agents [37].

According to the clinical characteristics of the study population, the average age of patients in the RheoSTAT-CP0620 sepsis sub-study was 40.42±13.28 years. 69.66 % of the group were men. Majority of participants did not smoke (69.66 %) and did not drink alcohol (74.16 %). Comorbidities were reported in 27/89 (30.3 %) patients in the Rheosorbilact group. The majority of cases belonged to the classes "Infections and infestations" (7.9 %), "Heart disorders" (6.7 %), "Vascular disorders" (5.6 %).

Dynamics analysis of the score based on the analyzed scales revealed favorable changes on the background of Rheosorbilact use (fig. 2, 3; table 2).

Change in the total SOFA score on day 3 compared to the baseline

ITT population

At admission, the average SOFA value (± standard deviation) was 3.08±1.10 points, and on day 3 – 1.08±1.16 points (fig. 2). Consequently, the average change in the SOFA score on day 3 of treatment compared to the baseline level was 2.01±1.37 points (table 2).

Additional analysis revealed that changes in the mean SOFA value on day 3 in patients treated with Rheosorbilact were statistically significant compared to the values at admission ($p<0.001$).

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PP population

At admission, the average SOFA value (± standard deviation) was 3.04±1.07 points, and on day 3 – 1.03±1.11 points (fig. 3). Consequently, the average change in the SOFA score on day 3 of treatment compared to the baseline level was 2.03±1.36 points (table 2).

Change in the total APACHE II score on day 3 compared to the baseline

ITT population

At admission, the average APACHE II value (± standard deviation) was 7.57±3.72 points, and on day 3 – 3.36±2.79 points (fig. 2). The average change in the APACHE II score after 3 days of treatment was 4.24±3.76 points (table 2).

Additional analysis revealed that changes in the mean APACHE II value on day 3 in patients treated with Rheosorbilact were statistically significant compared to the values at admission (p<0.001).

PP population

At admission, the average APACHE II value (± standard deviation) was 7.30±3.66 points, and on day 3 – 3.36±2.79 points (fig. 3). The average change in the score was 4.26±3.66 points.

Change in the total SAPS II score on day 3 compared to the baseline

ITT population

At admission, the average SAPS II value (± standard deviation) was 15.62±7.20 points, and on day 3 – 12.42±5.16 points (fig. 2). The average change in the SAPS II score on day 3 compared to the baseline score was 3.40±5.30 points (table 2).

Additional analysis revealed that changes in the mean SAPS II value on day 3 in patients treated with Rheosorbilact were statistically significant compared to the values at admission (p<0.001).

PP population

At admission, the average SAPS II value (± standard deviation) was 15.20±7.10 points, and on day 3 – 12.26±5.16 points

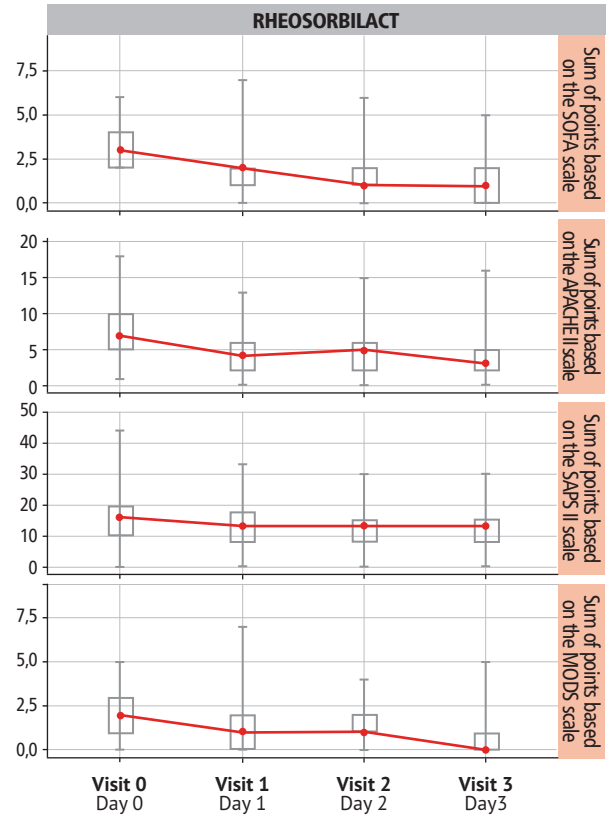

Fig. 2. Dynamics of scores on the scales SOFA, APACHE II, SAPS II and MODS in the ITT population

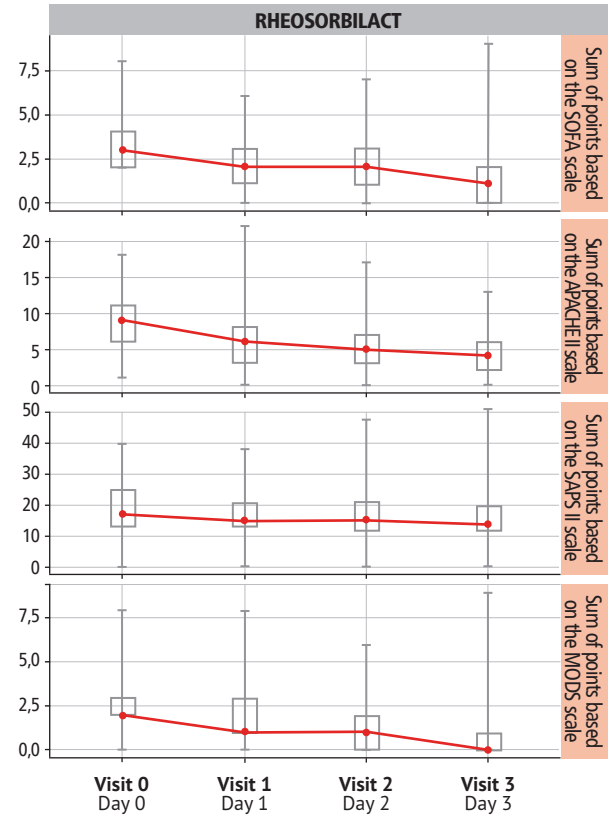

Fig. 3. Dynamics of scores on the scales SOFA, APACHE II, SAPS II and MODS in the PP population

Table 2. Changing in the score based on all applicable scales

Measures	Baseline	Level on day 3 of treatment	Average change	p
SOFA score	3.08±1.10	1.08±1.16	2.01±1.37	<0.001
APACHE II score	7.57±3.72	3.36±2.79	4.24±3.76	<0.001
SAPS II score	15.62±7.20	12.42±5.16	3.40±5.30	<0.001
MODS score	2.08±1.20	0.73±1.19	1.37±1.37	<0.001

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(fig. 3). Thus, the average change in the SAPS II score was 3.15±5.16 points.

Change in the total MODS score on day 3 compared to the baseline

ITT population

At admission, the average MODS value (± standard deviation) was 2.08±1.20 points, and on day 3 – 0.73±1.19 points (fig. 2). The average change in the MODS score on day 3 of treatment compared to the baseline level was 1.37±1.37 points (table 2).

Additional analysis revealed that changes in the mean MODS value on day 3 in patients treated with Rheosorbilact were statistically significant compared to the values at admission (p<0.001).

PP population

At admission, the average MODS value (± standard deviation) was 2.05±1.20 points. On day 3 of treatment, this indicator was 0.73±1.19 points (fig. 3). Thus, the average change in the MODS score was 1.36±1.41 points.

Additional analysis of changes in the studied parameters on day 3 of treatment compared to the baseline revealed that on the background of Rheosorbilact use there was not only a statistically significant decrease in the severity of multiorgan failure and severity of the condition based on all applied scales (SOFA, APACHE II, SAPS II, MODS II), but also a decrease in the severity of endogenous intoxication in accordance with the studied biochemical and immunological indicators, as well as an improvement in clinical parameters (a decrease in average body temperature and HR, an increase in systolic and diastolic BP, reduction of respiratory rate) (table 3).

It should be noted that already on day 3 of Rheosorbilact therapy, a decrease in the frequency of deviations in laboratory parameters of the function of elimination organs, blood glucose and electrolyte levels, including clinically significant ones, was observed (fig. 4). In particular, there was a decrease in the concentration of glucose (from 6.70 (5.60-8.45) to 5.50 (4.80-6.20) mmol/l), lactate (from 1.65 (1.00-1.91) to 1.55 (1.20-1.83) mmol/l), urea (from 5.24 (3.85-7.75) to 4.50 (3.70-6.20) mmol/l; p<0.001), creatinine (from 90.00 (69.67-112.50) to 76.28 (60.00-94.28) mmol/l; p<0.001), total bilirubin (from 13.80 (10.01-28.40) to 10.40 (8.10-13.70) mmol/l; p<0.001). ALT and AST concentrations did not change significantly.

In patients treated with Rheosorbilact, a significant decrease in the number of leukocytes (from 14.50 (11.00-17.10) to 8.80 (7.09-10.80) ×109/l; p<0.001), leukocytic II (from 5.12 (3.53-9.35) to 2.35 (1.33-4.22); p<0.001), nuclear II (from 0.19 (0.10-0.42) to 0.09 (0.04-0.15); p<0.001) and hematological II (from 5.29 (3.55-7.23) to 4.00 (2.54-5.25); p=0.002) was

Table 3. Measures of evaluation of Rheosorbilact efficacy before and after therapy

Indicators, units	Initial			On day 3			p
	n	Me	Midspread	n	Me	Midspread	
Sum of points based on the scale							
SOFA	79	2	2-4	78	1	0-2	<0.001
APACHE II	79	7	5-10	78	3	2-5	<0.001
SAPS II	79	16	10-19.5	78	13	8-15	<0.001
MODS	79	2	1-3	78	0	0-1	<0.001
Body temperature, °C	79	38.2	37.0-38.7	78	36.8	36.7-37.3	<0.001
HR, bpm	79	96	82-106	78	80	74.25-88	<0.001
Systolic BP, mm Hg	79	120	110-130	78	120	115-130	<0.001
Diastolic BP, mm Hg	79	70	60-80	78	80	70-80	<0.001
Respiratory rate per 1 min	79	20	18-22	78	18	16-20	<0.001
Urea, mmol/l	79	5.24	3.85-7.75	78	4.5	3.70-6.20	0.029
Creatinine, μmol/l	79	90	69.67-112.50	78	76.28	60.00-94.28	<0.001
Total bilirubin, μmol/l	79	13.8	10.01-28.40	78	10.4	8.10-13.70	<0.001
ALT, IU/l	79	25.0	12.25-38.85	78	24.5	9.48-36.60	0.194
AST, IU/l	79	26.5	13.10-48.62	78	29.0	12.32-36.98	0.363
Albumin fraction, %	14	52.65	42.00-57.98	14	54.65	49.10-57.65	0.327
C-reactive protein, mg/l	73	32.7	17.50-176.00	71	24.0	9.65-96.00	<0.001
Lactate dehydrogenase, U/l	74	301.5	197.25-406.25	70	235.75	180.50-312.50	>0.05
Platelets, $\times 10^9$/l	79	225	188.75-292.00	76	242.5	199.50-292.50	0.255
Leukocytes, $\times 10^9$/l	79	14.5	11.00-17.10	77	8.8	7.09-10.80	<0.001
Nuclear II	47	0.19	0.10-0.42	46	0.09	0.04-0.15	<0.001
Leukocytic II	40	5.12	3.53-9.35	44	2.35	1.33-4.22	<0.001
Hematologic II	40	5.29	3.55-7.23	44	4.0	2.54-5.25	0.002
Neutrophil/lymphocyte index	48	7.28	4.88-11.00	46	5.33	3.37-8.45	0.014
Excess of bases, mmol/l	67	-0.50	-3.75-2.10	66	1.20	-0.75-2.58	<0.001
Standard bicarbonate, mmol/l	63	23.8	20.75-25.30	62	24.3	23.25-26.35	0.013

Notes: data from the Rheostat-CP0620 RCT results report provided by "Yuria-Pharm"; n – number of observations; Me – median.

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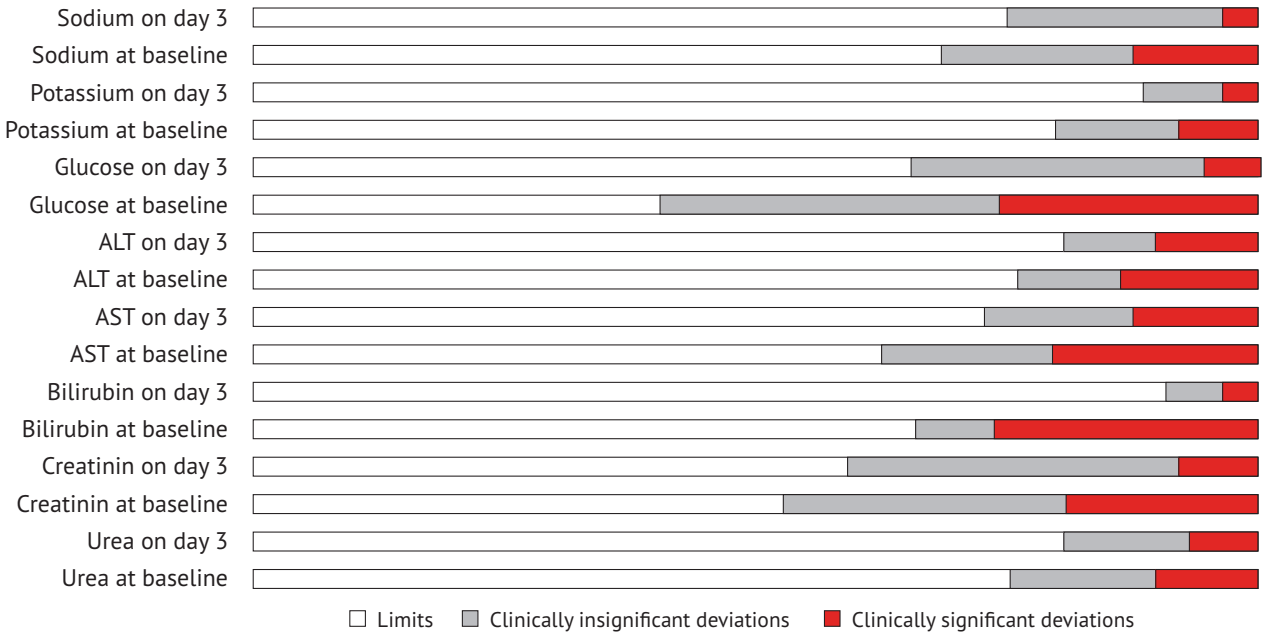

Fig. 4. Percentage of deviations in the function of elimination organs, glucose and blood electrolytes before and after a 3-day course of Rheosorbilact treatment

observed. The content of C-reactive protein also decreased (from 32.70 (17.50-176.00) to 24.00 (9.65-96.00) mg/l; p<0.001). At the same time the levels of immunoglobulins A (from 2.81 (1.63-4.03) to 2.89 (1.89-4.18) g/l), M (from 0.99 (0.60-1.14) to 1.10 (0.79-1.30) g/l) and G (from 11.03 (9.16-12.64) to 11.17 (8.75-15.54) g/l) increased. The neutrophil/lymphocyte ratio decreased from 7.28 (4.88-11.00) to 5.33 (3.37-8.45); p=0.014. This change is very important, since, according to the literature, the ratio reflects the activity of two universal pathogenetic mechanisms – systemic non-specific inflammation and immune system responses [21, 22].

Analysis of blood gas composition parameters revealed a statistically significant increase in the content of standard bicarbonate (from 23.23±3.47 to 24.11±5.51 mmol/l) and excess of bases (from -1.01±4.31 to 1.44±3.37 mmol/l) after 3 days of Rheosorbilact administration, which indicates a powerful alkalizing effect.

The average HR at admission was 93.15±17.69 bpm, and on day 3 of treatment – 80.61±11.28 bpm (p<0.001). A small but significant increase in systolic BP (from 120.00 (110.00-130.00) to 120.00 (115.00-130.00) mm Hg); p=0.015) and diastolic BP (from 70.00 (60.00-80.00) to 80.00 (70.00-80.00) mm Hg; p<0.001) was recorded. These changes may indicate an improvement in the cardiovascular system functioning, in particular, an increase in cardiac output. The median body temperature decreased from 38.20 (37.00-38.70) to 36.80 (36.70-37.30) °C (p<0.001), which indicates a pronounced decrease in intoxication syndrome. Another favorable sign is a decrease in the respiratory rate, which was observed during Rheosorbilact treatment: the initial indicator was 20.00 (18.00-22.00) per 1 min, and the indicator on day 3 of treatment was 18.00 (16.00-20.00) per 1 min (p<0.001).

During the study, AEs were registered in 20 patients (22.47 %). A total of 46 AEs were observed, 33 of which were mild in severity. None of the AEs, including two reported serious cases were associated with Rheosorbilact use.

In general, obtained results indicate that Rheosorbilact effectively improves patients' condition, reducing the severity of multiorgan failure and endogenous intoxication on the basis of the most indicators evaluated in the study in patients with sepsis.

Conclusions

As of now, the question of optimal infusion therapy in sepsis remains open. Various studies show that the tactics of aggressive large-volume infusion therapy are inferior to the tactics of low-volume infusion therapy with the use of special multifunctional multicomponent solutions. In particular, IT with Rheosorbilact (200-400 ml/day for 3 days) makes it possible to increase the volume of circulating blood on the background of a decrease in the total volume of infusion necessary to achieve a therapeutic effect, thus eliminating the risk of excessive hydration and fluid overload, which is especially important for patients in critical condition. Exogenous lactate in the composition of Rheosorbilact does not affect the level of endogenous lactate, which proves an excellent safety profile of the use of this solution. AEs observed during the study were not associated with the Rheosorbilact use. Inclusion of Rheosorbilact in the intensive care complex contributed to a decrease in temperature, HR and the number of leukocytes that serve as markers of endogenous intoxication. Rheosorbilact use for the first 3 days of intensive care provided an increase in the indicators of standard bicarbonate and excess of bases, that is, it reduced the likelihood metabolic acidosis development. It should be noted that to achieve the effects of Rheosorbilact, obtained during the study, it is necessary to adhere to the appropriate dose, rate and frequency of administration according to the prescribing information. The RheoSTAT-CP0620 study justifies the feasibility of Rheosorbilact use in the complex therapy of sepsis.

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